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DIVISION OF NARCOTIC DRUGS

Geneva

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The position of preparations of narcotic drugs under the narcotics treaties, with special reference to "exempted preparations"

Correspondence between governments, other interested authorities and the Secretariat of the United Nations has indicated that the treaty régime relating to preparations of narcotic drugs has given rise to certain problems of interpretation, and that this is apparently due to the variety of régimes applying to different types of preparations, as well as to difficulties resulting from the terminology used in the narcotics treaties. It may for this reason be useful to publish the following account of the treaty position of preparations of narcotic drugs.

I. The Term "Preparations"

The use of terms in the narcotics treaties, concluded as they were at different times, and having as authors many persons of different linguistic backgrounds, is often not fully consistent. This applies in particular to the term "preparations". The narcotics treaties refer by this term not only to preparations in the technical meaning of this word — i.e., to pharmaceutical preparations — but also to other substances. Pharmaceutical preparations of narcotic drugs may be defined as mixtures, solid or liquid, containing such drugs.[1]

II. Preparations other than Pharmaceutical Preparations

Substances which technically are not preparations, but which are referred to in the narcotics treaties by this term, are:

(*a*) "Preparations made directly from raw or medicinal opium and containing more than 20% of morphine" (article 1, paragraph 2, of the Convention for limiting the manufacture and regulating the distribution of narcotic drugs, signed at Geneva on 13 July 1931) (subsequently referred to as the "1931 Convention").

Such "preparations" are "drugs" for the purposes of the 1931 Convention and as between Parties thereto, also for purposes of the International Opium Convention signed at Geneva on 19 February 1925 [2] (subsequently referred to as the "1925 Convention") and subject to all the control provisions of these conventions applicable to "drugs".

(*b*) "Preparations made direct from the coca leaf and containing more than 0.1% of cocaine" (article 1, paragraph 2, of the 1931 Convention).

The position of these "preparations" (as "drugs") under the 1925 and 1931 Conventions is the same as that of the preparations mentioned under (*a*).

(*c*) "Galenical preparations (extracts and tinctures) of Indian hemp" (cannabis) (article 4 (*f*) of the 1925 Convention).

Such "preparations" are "drugs" for the purpose of the provisions of the 1925 Convention and generally speaking subject to the same provisions of this convention as morphine. The 1931 Convention does not apply to them.

The following differences between the régime governing such drugs as morphine and that governing the extracts and tinctures may, however, be noted under the terms of the 1925 Convention: annual statistical returns (article 22, paragraph 1 (*b*) of the 1925 Convention) on the manufacture of morphine but not of extracts and tinctures of cannabis are required. The premises on which morphine is manufactured must be licensed. This requirement does not apply to the cannabis extracts and tinctures (article 6 (*a*) in connexion with article 4 of the 1925 Convention). The situation is exactly reversed for *preparations* (i.e., pharmaceutical preparations) of these drugs. The requirement of licensing premises applies to the preparations of extracts and tinctures of cannabis (i.e., to the preparations of the "galenical preparations" of cannabis) but not to morphine preparations. Annual statistical returns on manufacture must be furnished for the preparations of cannabis extracts and tinctures but not for morphine preparations. This somewhat peculiar situation is due to the fact that the preparations of the extracts and tinctures of cannabis were placed under the control régime of the 1925 Convention by operation of article 10 thereof (articles 4 (*g*), 6 (*a*), and 22, paragraph 1 (*b*) of this Convention). Preparations of cannabis extracts and tinctures which are capable only of external use are not subject to international control.[3] The fact that under the terms of the 1925 Convention the preparations of cannabis extracts and tinctures are subject to a more severe régime than the basic drugs is, however, not reflected in national legislations or in the practice of the Permanent Central Opium Board.[4]

(*d*) "Ordinary preparations of which the resin [5] forms the base (such as hashish, esrar, chiras, djamba)" (article 11, paragraph 1 (*a*), of the 1925 Convention).

As indicated by the samples, these "ordinary preparations" are generally simply the crude resin as separated by mechanical means,[6] and unless mixed with other substances are not pharmaceutical preparations as defined above.

The "ordinary preparations" are not subject to the general régime provided by the 1925 Convention for narcotic drugs and their (pharmaceutical) preparations. They are, however, subject to the provisions of Chapter V of this Convention, relating to the control of international trade, and to those of article 11, paragraphs 1 (*a*) and 2 concerning the requirement of a "special import certificate" and the "effective control of such a nature as to prevent the international illicit traffic". The annual statistical returns on the narcotic substances which have been confiscated on account of illicit import and export and the quarterly import and export statistics (article 22, paragraph 1 (*e*) and paragraph 2 of the 1925 Convention) must also include the ordinary preparations.[7]

[1] United Nations document E/CN.7/AC.3/9, para. reference number 28.
[2] See article 13, para. 1 (*a*) of the 1931 Convention.
[3] League of Nations circular letters: CL.161.1936.XI; CL.161.(a). 1936.XI; CL.99.1939.XI; CL.99.(a).1939.XI; and CL.161.1939.XI.
[4] See Statistical Form of the Permanent Central Opium Board, C/2.
[5] i.e., cannabis resin.
[6] *Bulletin on Narcotics*, Volume II, No. 2, English edition, pp. 35 and 42.
[7] Forms A. 1 and E of the Permanent Central Opium Board.

The special measures provided for in articles 24 and 26 of the 1925 Convention can also be applied if the dangerous situations mentioned therein arise in respect of the " ordinary preparations ".

III. Pharmaceutical Preparations

This article will not deal with such mixtures containing " raw opium ", " prepared opium ", coca leaves, cannabis and cannabis resin as are destined for pleasure — i.e., for purposes other than medical or scientific. As the basic drugs which they contain, these mixtures which strictly speaking would be covered by the above definition of pharmaceutical preparations are not subject to the full control régime applicable in general to narcotic drugs, but only to limited régimes differing in the case of each of the drugs.

It is, however, believed that preparations of opium of any kind (including " raw opium " and " prepared opium ") and of coca leaves enjoy this privileged position only within the limits necessary to facilitate the tolerated practices of opium smoking, opium eating and coca leaf chewing. Depending on their morphine or cocaine content, they must otherwise be considered to be subject to the régime by which preparations containing these drugs would be governed.

The term " medicinal opium " [8] includes opium processed in a certain way in accordance with the requirements of the national pharmacopoeias, whether mixed with neutral materials or not. If so mixed, " medicinal opium " would constitute a pharmaceutical preparation as defined above. In its pure or mixed forms, " medicinal opium " is not governed by the régime provided by the 1925 Convention for morphine, but by that applicable to morphine preparations — i.e., the requirements of licensing premises of manufacture and of furnishing manufacturing statistics do not apply to " medicinal opium ".

The term " exempted preparations ", although commonly used, is not a treaty term. When one employs this term, one refers generally to those (pharmaceutical) preparations which by reason of their small narcotics content are by express treaty clause or by specific decision of the Health Committee of the League of Nations (World Health Organization) exempted from the provisions of the 1925 Convention.[9] Preparations adapted to a normal therapeutic use of drugs subject to the régime applicable to drugs in Group II of article 1, paragraph 2, of the 1931 Convention (subsequently referred to as drugs of Group II) are also often called "exempted preparations ", since, in accordance with article 13, paragraph 2, of the 1931 Convention, as interpreted by the Advisory Committee (of the League of Nations) on the Traffic in Opium and Other Dangerous Drugs (subsequently referred to as the Opium Advisory Committee) [10] and apparently also by the parties to this convention, they are not subject to the control provisions of the 1925 Convention. The 1931 Convention refers to such " exempted preparations " [11] as " preparations for the export of which export authorizations are not required ".[12]

The term " preparations for the export of which export authorizations are not required ", as well as the term " exempted preparations " are, however, somewhat misleading. The first term seems to be too narrow, the second one too broad. The preparations concerned are, on the one hand, exempted from more control provisions than those requiring the application of the import certificate and export authorization system, and on the other hand, are exempted only from the provisions of the 1925 Convention but not from those of the 1931 Convention, including the provisions aiming at the world-wide limitation of the supplies of narcotic drugs (manufacture and import) to the amounts needed for medical and scientific purposes (estimate system).

The term " exempted preparations " may also not be very appropriate for the preparations of cannabis extracts or tinctures capable only of external use. They are not subject to the control provisions of the 1925 Convention nor to those of the 1931 Convention which, in its turn, does not deal with cannabis or its products. The Health Committee of the League of Nations declared in 1939 that its recommendation adopted in 1935 in accordance with article 10 of the 1925 Convention to place preparations of cannabis extracts and tinctures under the international control system provided for by that convention did not apply to preparations which were capable of external use only. Whether this declaration constitutes an " exemption " under article 8 of the 1925 Convention appears to be a matter of doubt.[13]

Leaving aside the special régimes provided by the international narcotics treaties [14] for raw opium, coca leaves, cannabis and cannabis resin in their pure forms, or in appropriate mixtures for non-medical consumption in such tolerated practices as opium smoking, opium eating, coca leaf chewing, smoking or eating of cannabis, and limiting oneself to an examination of the provisions of the general narcotics régime such as is established for the control of narcotic drugs and their preparations intended for medical and scientific purposes, one finds that the only preparations free — or if one wishes to say " exempt " — from international control are the preparations of extracts and tinctures capable only of external use. All other (pharmaceutical) preparations of narcotic drugs, including the so-called " exempted preparations " are subject to various régimes of differing rigidity as follows:

[8] Article 1 of the 1925 Convention and article 1, para. 3, of the 1931 Convention.

[9] Or — a not very practical case — (by express treaty clause) from the provisions of the International Opium Convention, signed at The Hague on 23 January 1912 (subsequently referred to as the " 1912 Convention ").

[10] League of Nations document C.191.M.136.1937.XI, para. 135, English edition, p. 175.

[11] i.e., to the preparations exempted from the provisions of the 1925 Convention, not to those exempted from the 1912 Convention.

[12] See article 5, para. 2 (*a*); article 6, para. 1 (*a*); article 14, para. 3 (*g*); article 17 (last sub-paragraph); and article 22 of the 1931 Convention. See also Form of the Permanent Central Opium Board, B/2.

[13] League of Nations documents CL.99.1939.XI; CL.99 (a).1939.XI; CL 161.1939.XI; and CH.1396. From the relevant report of the Office international d'Hygiène publique, and from the communication by the Council of the League of Nations of this decision under article 10 of ihe 1925 Convention, it would appear that the action relating to preparations capable of external use only was one of clarifying the earlier decisio tnaken under this article recommending the control of cannabis extracts and tinctures (CL.161.1936.XI), rather than an exemption taken under article 8 of the Convention.

[14] i.e., the 1912 and 1925 Conventions. See also the Agreement concerning the Manufacture of, Internal Trade in and Use of Prepared Opium, signed at Geneva on 11 February 1925, and the Agreement for the Control of Opium Smoking in the Far East, signed at Bangkok on 27 November 1931.

(a) *Diacetylmorphine preparations*

The most rigidly controlled preparations are those containing diacetylmorphine. They are not only subject to all the standard provisions of the 1925 Convention applying to preparations of drugs belonging to Group I of article 1, paragraph 2, of the 1931 Convention (subsequently referred to as drugs of Group I), such as morphine, but in addition to the special export restrictions of article 10 of this Convention, according to which their export is prohibited except to a country in which diacetylmorphine is not manufactured, at the request of the government of such a country. The request must be accompanied by an import certificate; the quantities exported must be limited to such amounts as are necessary for the medical and scientific needs of the importing country and must be consigned to the government department indicated in the certificate. The imported preparations must be distributed by and on the responsibility of the government of the importing country. In view of the opinion of the World Health Organization that diacetylmorphine is not necessary for medical practice, some consideration might be given to the question whether, under article 10 of the 1931 Convention, any export of diacetylmorphine preparations (and, of course, of the basic drug itself and its salts) for other than scientific purposes (including clinical experiments) could be considered legal.

(b) *Preparations of drugs of Group I*

The international régime applicable to them is in general the same as that governing the basic drugs of Group I. Premises on which such preparations are being manufactured need, however, not be licensed.[15] Statistics on the manufacture of the preparations need not be furnished to the Board.[16]

(c) *Preparations of drugs of group II other than those adapted to a normal therapeutic use*[17]

Such preparations are subject to the same régime as the basic drugs which they contain if one adopts the interpretation given by the Opium Advisory Committee to article 13, paragraph 2, of the 1931 Convention.[18] This would mean that as far as the provisions of the 1925 Convention are concerned, these preparations are subject to the control provisions governing the manufacture of and wholesale and international trade in narcotics drugs, but not to those relating to the (domestic) retail trade.

(d) *Tincture of opium, Sydenham laudanum and Dover powder*

These preparations, depending on their morphine content, are in principle subject to the same international régime as morphine preparations, but any Party may authorize chemists to supply them to the public, at their own discretion, as medicines, for immediate use in urgent cases. The maximum dose which may be supplied must not contain more than 25 centigrammes of officinal opium, and the chemist must enter in his books the quantities supplied (article 9 of the 1925 Convention).

(e) "*Exempted preparations*"[19]

With the reservations mentioned above, we understand under this term the following groups of preparations:

(i) Preparations which, because of their small narcotics content, are, by express treaty provisions, automatically exempted from the control régime of a particular narcotics treaty;

(ii) Preparations expressly exempted under article 8 of the 1925 Convention by decisions of the Health Committee of the League of Nations (World Health Organization);

(iii) Preparations of drugs of Group II adapted to a normal therapeutic use.

(i) *Preparations which, because of their small narcotics content, are, by express treaty provisions, automatically exempted from the control régime of a particular treaty*

The preparations are differently defined by related provisions of the 1912 Convention, the 1925 Convention, and the 1931 Convention, each subsequent treaty applying more rigid standards.

(aa) *1912 Convention*

According to article 14 (*b*) and (*c*) of the 1912 Convention, Parties are not required to apply to preparations containing not more than 0.2% of morphine, 0.1% of cocaine, or 0.1% of diacetylmorphine the control required under this Convention for the manufacture, import, sale or export of opiates and cocaine.

The automatic exemptions granted by the 1912 Convention are of little, if any, practical importance. The relevant provisions of this treaty were replaced by the provisions of the 1925 Convention as between Parties thereto.[20] They seem also to have ceased to be in force for Parties to the 1912 Convention who, although not Parties to the 1925 Convention, have become Parties to the 1931 Convention.[21] Very few Parties to the 1912 Convention are Parties neither to the 1925 Convention nor to the 1931 Convention.

(bb) *1925 Convention*

In view of the provisions of article 4 (*d*), the control régime of the 1925 Convention governing manufactured narcotic drugs, or for that matter any other control provisions of this convention, do not apply to preparations containing not more than 0.2% of morphine or 0.1% of cocaine. There is no automatic exemption for diacetylmorphine preparations.

The control provisions of the 1912 and 1925 Conventions from which automatic exemption is respectively granted cover the same ground — i.e., administrative control of national and international

[15] Para. 6 (*a*) of the 1925 Convention.

[16] Article 22, para. 1 (*b*), of the 1925 Convention.

[17] i.e., in case of preparations of codeine and ethylmorphine (dionine): dry preparations (pills, tablets, etc.) containing more than 0.1 g of either substance and solutions containing more than 10% might be considered not to be "adapted to a normal therapeutic use". See Report of the Health Organization to the Council on the work of the twentieth session of the Health Committee (League of Nations document C.652.M.312. 1933.III, p. 6).

[18] League of Nations document C.191.M.136.1937.XI, para. 135, p. 175 of the English edition.

[19] As regards preparations of cannabis extracts and tinctures capable only of external use, see above.

[20] Article 31 of the 1925 Convention.

[21] Article 13, para. 1, of the 1931 Convention, in connexion with article 31 of the 1925 Convention.

trade; in particular, they do not relate to the estimate system for the limitation of narcotics supplies, a system governed by the 1931 Convention.

(cc) 1931 Convention

As between Parties to the 1931 Convention, the automatic exemption from the provisions of the 1925 Convention can only be granted to solutions or dilutions containing not more than 0.2% of morphine or 0.1% of cocaine, if they are compounded with an active (i.e., pharmacologically active) substance, liquid or solid. Morphine or cocaine preparations compounded only with an inert substance cannot be so exempted. Again there is no automatic exemption for diacetylmorphine preparations.

Since the automatic exemptions granted under the 1925 or 1931 Conventions apply only to obligations arising from the provisions of the 1925 Convention, it follows that the automatically exempted preparations are subject to the relevant provisions of the 1931 Convention as well as to those of the Convention of 1936 for the Suppression of the Illicit Traffic in Dangerous Drugs (subsequently referred to as the " 1936 Convention ") and thus not " exempted from international narcotics control ".[22]

ii) *Preparations expressly exempted under article 8 of the 1925 Convention*

Under the original (unamended) text of the 1925 Convention, the Health Committee of the League of Nations was authorized, after consulting the Permanent Committee of the Office international d'Hygiène publique, to exempt from the provisions of this convention narcotic drug preparations which cannot give rise to drug addiction (" drug habit ") on account of the medicaments with which the narcotics drugs concerned were compounded and which, in practice, precluded the recovery of the narcotic drugs. This right of the Health Committee was transferred to the World Health Organization by the Protocol signed at Lake Success on 11 December 1946.[23] This Organization, under article 8 of the 1925 Convention as amended by this Protocol, must consult the " expert committee appointed by it ".

The Health Committee of the League of Nations exempted a number of preparations. The World Health Organization exempted several Ipecopan preparations which it seems, however, were already automatically exempted under the relevant treaty provisions.[24] A list of preparations exempted by application of article 8 was recently published in Schedule III of the Third Draft of the Single Convention on Narcotic Drugs, which was completed by the Commission on Narcotic Drugs at its thirteenth session, in spring 1958.[25]

It may be noted that preparations of drugs of Group II cannot be exempted by operation of article 8 of the 1925 Convention.[26] Such an exemption seems, however, not to be necessary. If the preparations are "adapted to a normal therapeutic use" they enjoy in general the same privileged position of exemption as preparations exempted by virtue of article 8 of the 1925 Convention. If they are, however, not so adapted there seems to be hardly any need for exemption, in particular also because the provisions of the 1925 Convention governing the (domestic) retail trade do not apply to them.

Preparations exempted by virtue of article 8 of the 1925 Convention are subject to the same régime as préparations exempted automatically by the specific provisions of the 1925 and 1931 Conventions. This means they are only exempted from the provisions of the 1925 Convention, but not from those of the 1931 and 1936 Conventions.

In theory, some legal problems may arise from the fact that the 1925 Convention is in force in its amended[27] as well as its unamended form and that under the unamended text of its article 8 it was the now defunct Health Committee of the League of Nations which was granted authority of exemption, while under the amended text the World Health Organization holds this power. It is, however, the view of the World Health Organization, not disputed by governments, that States, whether Parties to the unamended or amended[27] 1925 or 1931 Convention, may make use of all exemptions — of those granted by the Health Committee, as well as those granted by the World Health Organization. It was therefore not found to be necessary for the World Health Organization to repeat, for the benefit of States Parties to the amended Conventions, exemptions granted by the Health Committee of the League of Nations.

It seems that in the light of later experience some of the exemptions granted by the Health Committee of the League of Nations have not proved to be justified. It cannot be excluded for the future that, in the light of the evidence available at the time, exemptions may again be granted, which, by later experience, may prove to be harmful to public health. The text of article 8 in its unamended as well as its amended form does not expressly provide for authority to rescind exemptions once granted. It may, however, be considered on more general legal grounds whether, despite the lack of such an express provision, the World Health Organization does not have this authority. If — as seems to have been widely assumed — the exemptions granted are considered to be irrevocable, it may tend to induce the World Health Organization to be more reserved in granting exemptions than would otherwise be necessary, and this may not constitute a desirable situation from the viewpoint of some national administrations. When the Health Committee of the League of Nations omitted several preparations, exempted earlier, from its Recapitulatory List of Preparations exempted from the Provisions of the International Opium Convention by Application of Article 8 of that Convention,[28] it seems that at least some of its members assumed that the Committee had authority to rescind an exemption granted under article 8.

[22] For preparations of cannabis extracts and tinctures capable of external use only, see above. Such preparations are " exempted from international narcotics control ".

[23] See also Protocol of 22 July 1946 concerning the Office international d'Hygiène publique.

[24] *World Health Organization Technical Report Series* No. 57, English edition, p. 4; see article (*d*) of the 1925 Convention and article 13, para. 1 (*b*) of the 1931 Convention

[25] ECN.7/AC.3/9/Add.1, Schedule III, English edition, pp. 11-24; see also *Bulletin on Narcotics*, Volume III, No. 4, pp. 2-8

[26] Article 13, para. 2, of the 1931 Convention.

[27] i.e., by the Protocol signed at Lake Success on 11 December 1946.

[28] League of Nations document C.114.M.54.1932.III.

It may also be noted that while decisions to place a drug under full international control must be initiated by a government,[29] decisions to exempt a preparation from the provisions of the 1925 Convention, under (the amended) article 8 thereof, may be adopted by the World Health Organization on its own authority.[30]

(iii) *Preparations of drugs of Group II adapted to a normal therapeutic use*

If the somewhat obscure provisions of article 13, paragraph 2, of the 1931 Convention are interpreted in accordance with the views of the Opium Advisory Committee, such preparations are exempted from the provisions of the 1925 Convention.[31] They are, in general, subject to the same régime as the preparations exempted by virtue of article 8 of the 1925 Convention. In some places of the 1931 Convention the term " preparations for the export of which export authorizations are not required " applies to preparations of drugs of Group II adapted to a normal therapeutic use, as well as to preparations exempted by specific treaty provisions or by operation of article 8 of the 1925 Convention from the provisions of this Convention.[32] In other cases, however, this term does not include the preparations of drugs of Group II.[33] It is held that Parties to the 1931 Convention need not include in the annual statistics furnished by them to the Permanent Central Opium Board the amounts of drugs of Group II used by manufacturers and wholesalers for the compounding of preparations adapted to a normal therapeutic use, while such information must be supplied in respect of preparations exempted from the 1925 Convention either by express treaty provisions or under article 8 of this Convention.[34] Similarly, the Permanent Central Opium Board need not include in its annual statement[35] the amount of drugs of Group II used for the compounding of preparations adapted to a normal therapeutic use, although this information must be given for other preparations exempted from the 1925 Convention.[36] Preparations of drugs of Group II adapted to a normal therapeutic use are, of course, subject to the other relevant provisions of the 1931 Convention as well as to those of the 1936 Convention.

It can be seen that the provisions relating to the control of preparations of narcotic drugs in general, and to the so-called exempted preparations in particular, are varied and complicated. Such differences as exist were not necessarily motivated by substantive considerations but are frequently due to drafting defects often caused by the conditions of pressure under which the relevant provisions were drafted and adopted. The obscurities, complexities and differences are, however, not of great practical importance. Of the various standards which, under the treaty provisions, would literally be applicable to different Parties, only the highest ones are generally used in national practice. It may be said that a State which would not conform with the higher requirements would hardly escape criticism by reference to the fact that it is only bound by the lower standards. This may reasonably be expected — e.g., in the case of a government which is a Party to the 1925 Convention but not to the 1931 Convention and which, in accordance with article 4 (*d*) of the 1925 Convention, would grant automatic exemption to a preparation containing not more than 0.2% of morphine or not more than 0.1% of cocaine, unless the preparation is compounded with an active substance as required by article 13, paragraph 2, of the 1931 Convention. The exact grounds, whether legal or otherwise, on which such a government may expect criticism need not be examined here. The expectation is based on the experience in a great number of cases in which governments actually have been subject to criticism because they have not applied higher standards set by later narcotics treaties to which they have not formally become Parties.

[29] Article 11 of the 1931 Convention; and article 1 of the Protocol of 19 November 1948 for bringing under international control drugs outside the scope of the 1931 Convention.

[30] It may, however, be mentioned that under article 10 of the 1925 Convention, as amended, the World Health Organization may, on its own initiative, place a drug under the control provisions of this Convention.

[31] League of Nations document C.191.M.136.1937.XI, para. 135, English edition, p. 175.

[32] Article 5, para. 2 (*a*); article 6, para. 1 (*a*); and article 17, last sub-para., of the 1931 Convention.

[33] Article 14, para. 3 (*g*) and article 22 of the 1931 Convention.

[34] Article 22 of the 1931 Convention.

[35] Article 14, para. 3 (*g*) of the 1931 Convention.

[36] League of Nations document C.191.M.136.1937.XI, paras. 154 and 193, English edition, pp. 189 and 213.

The use of meprobamate in the treatment of heroin withdrawal symptoms [1, 2, 3]

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Although addiction to narcotic drugs is common in many areas of the world, ethnological, economic and social factors present in Hong Kong make this a problem of considerable importance in this locality. Prior to 1945 the use of narcotics in this area was confined mainly to the smoking of opium. An analysis of the amounts and manner in which opium was employed and the effects produced by its use suggests that many individuals did not consume sufficient opium to become severely addicted; and, in consequence, the use of opium did not constitute as grave a problem as that at present produced by the consumption of heroin. The smoking of opium has gradually been replaced by the use of heroin, which is now the chief narcotic employed in this area. This change has been accompanied by a marked increase in the use of narcotics by members of the lower income bracket. Numerous addicts spend between 75% and 90% of their income on heroin, and are, therefore, unable to afford adequate food, clothing and shelter for themselves and their families.

Various reasons are given by addicts to explain their initial use of heroin. Some claim that they originally took heroin to relieve mild chest or abdominal pains. Others state that the use of heroin enables them to "work harder for longer periods of time". Still other addicts claim they were introduced to the use of heroin by "bad friends". It is recognized that many of the factors which prompted an individual to begin the use of heroin are also responsible, in part at least, for the continued use of this drug. However, the occurrence of marked withdrawal symptoms following cessation of drug intake represents an additional factor which promotes the further use of heroin. It is felt that, if the withdrawal symptoms could be prevented or markedly alleviated, many individuals might be induced to discontinue the use of narcotics.

Many agents and methods have been employed in the attempt to decrease the severity of the abstinence syndrome (Goodman & Gilman, 1955). These include substitution therapy with methadone, the use of pyrogens, antipyretic analgesics, sedatives (such as paraldehyde, barbiturates or bromides), stimulants (caffeine or amphetamine), anti-cholinesterases, purgatives, anti-diarrhoeal agents, hypertonic glucose or sucrose, calcium or magnesium ions, blistering and various hormonal preparations including insulin, parathormone, adreno-corticotropic hormone and cortisone. The use of so many different substances, many of which have opposing actions, indicates that previous methods of treatment failed to provide rapid relief of the withdrawal suffering.

Recently, both phenothiazine derivatives (Aivazian, 1955; McMahon, 1957; Friegdood & Ripstein, 1955; Hedqvist, 1954; Sainz, 1957) and meprobamate (Thimann & Gauthier, 1956) have been employed to treat narcotic withdrawal symptoms. Unfortunately, the published results do not clearly indicate the value of these drugs in the treatment of the abstinence syndrome, since, in general, other drugs were administered simultaneously, and the symptoms were not evaluated quantitatively; nor were adequate controls employed. For example, Friedgood & Ripstein (1955) used chlorpromazine in the treatment of five morphine and two demerol (pethidine) addicts whose addiction had followed the medical use of these agents. They reported that the administration of relatively large doses of chlorpromazine following the abrupt withdrawal of the addicting drug prevented the "phenomena that constitute the abstinence syndrome". The patients slept most of the time during the first three days of therapy, and were given intravenous fluids and vitamins concurrently. Although it is likely that the marked "psychomotor-sedative" effect of chlorpromazine was of value, the lack of controls makes it difficult to determine the degree of benefit afforded by this treatment.

In Malacca a regimen has been adopted for the treatment of opium addicts which includes the use of chlorpromazine (McMahon, 1957). In addition, phenobarbitone, butobarbitone, thiamine and amphetamine are employed in the treatment. Although the schedule utilized "proved adequate for most of the patients seen", the lack of data regarding the severity of the symptoms, the use of multiple drugs and the omission of controls make it difficult to evaluate the effects of chlorpromazine in this study.

[1] We wish to thank Mr. C. J. Norman, Commissioner of Prisons, and Dr. D. J. M. Mackenzie, Director of Medical and Health Services, for their permission to conduct this study. In addition, we would like to acknowledge the kind co-operation of Superintendent T. G. Garner, Chief Officer E. M. Gemmell and the other officers and staff of H.M. Prison, Victoria, whose assistance materially facilitated this investigation. Finally, we would like to express our appreciation to Senior Superintendents A. A. Shaw and T. Cashman and Superintendents A. A. Baggott and J. F. Ferrier, of the Police Anti-corruption and Narcotics Bureau, for their aid in the investigation of many facets of the addiction problem.

[2] The meprobamate ("Miltown") and placebos employed in this study were kindly supplied by the Lederle Laboratories Division of the American Cyanamid Company, New York.

[3] The opinions expressed in this paper are those of the authors, and do not necessarily reflect the views of the Hong Kong Government.

Thimann & Gauthier (1956) noted " moderate " improvement in three out of four heroin addicts treated with meprobamate after gradual withdrawal of the narcotic. Controlled studies employing placebos in heroin addicts were not reported, so it is difficult to ascertain whether the improvement noted was due to the effects of meprobamate or merely due to the passage of time. It was therefore deemed desirable to conduct a controlled study of the effect of meprobamate in the treatment of the abstinence syndrome.

Subjects and Methods

Fifty-one male patients were included in this study. The individuals were selected during the initial medical examination of inmates shortly after their admission to H. M. Prison, Victoria, Hong Kong. Since approximately forty to fifty addicts are admitted to prison daily, rigid criteria could be adopted for the selection of subjects. Except for six healthy non-addicts employed to evaluate the effects of large doses of meprobamate in normal individuals, all subjects selected had been addicted to heroin for more than eighteen months. The maximum duration of heroin consumption encountered among these subjects was fifteen years, while the average period of use was six years and a half. Nearly half of the addicts selected had used opium for periods ranging between three and forty years (average, eleven years) prior to their employment of heroin.

All addicts selected spent at least HK $4 (5*s*.) per day for heroin. The maximum daily expenditure by a member of this group was HK $15 (19*s*.), while the average outlay for heroin by the addicts included in this study was about HK $7.50 (8*s*. 6*d*.) per day. The cost of heroin varies with the availability of the drug and the quality of the product. The various grades employed in smoking (No. 2 and No. 3 powders) (" yee ho faan, saam ho faan ") usually cost HK $5-7 per g. Chemical analysis of " medium grade " samples indicates that this material contains approximately 87%-92% diacetylmorphine hydrochloride (Gruhzit, 1958). Therefore the " smokers " in this study used an average of about 1.1 g per day of this heroin salt. It is estimated that, in the process of smoking, between 50% and 75% of the heroin is absorbed (Gruhzit, 1958). More purified grades of heroin employed for intravenous use cost approximately HK $8-10 per g, but probably provide the user with a greater intake per dollar than that obtained by smokers who use cheaper grades of heroin.

The addicts who participated in this study had been in police custody and had appeared before the appropriate judicial official prior to their medical examination. Therefore, all addicts who were selected had abstained from the use of narcotics for 46-72 hours prior to the onset of treatment. Although this time lapse made the testing of the ability of drug therapy to prevent withdrawal symptoms infeasible, the marked abstinence syndrome which usually occurs within two to three days after heroin withdrawal facilitated the selection of patients.

Marked withdrawal symptoms were exhibited by all addicts selected for meprobamate evaluation. Individuals who met the criteria discussed and who also, in the opinion of the observers, appeared to be suffering from marked abstinence symptoms, were asked to describe their illness. Only those who voluntary mentioned the majority of the " major " symptoms were chosen for study. Although it is recognized that some otherwise suitable subjects may have been excluded by this method of selection, it was felt that " prompting " might result in false answers. After selection the patients were extensively questioned regarding the severity of their various symptoms.

As far as could be determined, all persons included in this study were, except for withdrawal symptoms, in relatively good health. Many of the addicts also suffer from tuberculosis, chronic nephritis, gastric ulcers and other major illnesses. Individuals who had a history of any major illness or who showed signs of any serious disease were excluded as subjects for this evaluation. As a further precaution, physical examination and routine urinalysis were done on all subjects.

Care was also taken to select, so far as possible, subjects who would answer questions truthfully. Because many individuals prefer hospitalization to hard labour, and because individuals with even moderate withdrawal symptoms desire treatment, there was a tendency for some of those interviewed to exaggerate their amount of heroin consumption. This was noted especially after this study had been in progress for several weeks, and the information had spread among the inmates that " kai pak faan yuen ", or " anti-heroin drug " was available. However, the veracity of the addicts could be checked in various ways. The amount of money claimed to be spent on heroin was compared with the individual's income and family status. The average unskilled labourer earns about HK $3-6 per day. Therefore, unless he has an outside source of income, it is impossible for him to spend more than this amount on narcotics. Unfortunately, many of the addicts do spend up to 90% of their income on heroin. The hands and fingers of the individuals were also examined carefully. Addicts who smoke heroin, as will be described later, usually have marked staining of the fingers and signs of frequent burns. The failure of addicts who claimed to smoke large amounts of heroin to exhibit these signs cast doubt on their truthfulness. The arms of addicts who employed heroin intravenously were examined for signs of sclerosed veins. Lack of sufficient damage to the veins excluded from participation in this study individuals who claimed to have taken heroin intravenously for several years. Since practically all addicts in this area who consume large amounts of heroin for long periods of time suffer a loss of weight ranging from 15 lb to 40 lb, obesity also disqualified a person as a subject in this experiment. Finally, although there is considerable variation in the severity of withdrawal symptoms among individuals who have consumed similar amounts of narcotics, experience gained in the observation of thousands of addicts during the withdrawal period enables one to estimate the severity of addiction. Individuals were not selected if there was significant discrepancy between the estimated and claimed intake of heroin.

Various methods were employed by the addicts for the administration of heroin. Approximately 10% of the subjects

selected self-administered heroin intravenously. This percentage is at least twice that encountered in the general narcotic group in this area, but the increased expenditure and the increased severity of withdrawal symptoms which intravenous users experience influenced the selection of subjects.

Most of the remaining subjects either "chased the dragon" [4] (" chui loong ") or " played the mouth organ " (" chui hau kum "). Both of these methods of heroin usage are relatively similar. Several granules of No. 2 or No. 3 powder containing approximately 87%-92% diacetylmorphine hydrochloride are placed, together with approximately four times as much " base powder " (" dai faan "), on a trough formed from cigarette package tinfoil. The material is heated from below with matches or tapers and the ensuing fumes are inhaled. Originally a hollow tube about eight inches long and approximately one-quarter to three-eighths inches in diameter formed from bamboo or rolled-up paper was used to inhale the vapours which arose from the heated mixture. Because of the tendency of the molten mass to flow up and down the tinfoil trough, the source of the fumes also migrates. The moving trail of fumes resembles the classical Chinese concept of the undulating dragon's tail, and the term " chasing the dragon " is therefore employed to describe this method of smoking heroin.

From the addict's standpoint this method offers various advantages — the equipment required is easily obtained and cannot in itself be used to incriminate him. However, although it is estimated that the more adroit addict can inhale approximately 50%-75% of the fumes evolved from the mixture, the use of a narrow tube is relatively inefficient. A small matchbox cover is now usually substituted for the hollow tube, since its increased cross-sectional area facilitates the inhalation of a greater percentage of vapours. The resemblance of a matchbox cover to the musical instrument has resulted in this method's being known as " playing the mouth organ ".

Since heroin granules have a tendency to char and decompose when heated, it is necessary to employ a base powder, or " dai faan ", as a vehicle when heroin is smoked in the methods described above. Barbitone or, less frequently, phenobarbitone are commonly employed as base powder. These substances are readily volatilized and inhaled together with the heroin fumes. Previous investigation (Gruhzit, 1958) indicates that, in general, insufficient amounts of the base powder are inhaled by the average heroin addict to produce concomitant barbiturate addiction. However, individuals who smoke large amounts of heroin, and therefore employ large amounts of base powder, may have combined heroin-barbiturate addiction. It is likely that the increased incidence of " non-epileptic " withdrawal convulsions which has been observed since the introduction of barbitone as a base powder is the result of barbiturate addiction.

The remainder of the individuals selected for study (less than 10%) combined heroin usage with cigarette smoking. Granules of heroin imbedded in the tip of a cigarette are volatilized and inhaled as the cigarette is smoked. The cigarette must be held in a vertical position to prevent the heroin granules from falling out. Because of this position the use of heroin in this manner is known as " firing the ack-ack gun " (" dah fay gay "). Recently, various modifications in this technique have been noted. Some individuals employ a pipe-type cigarette holder which allows the cigarette to remain in a vertical position without tilting the head. In addition, the use of relatively pure heroin granules has been superseded in part by the use of a " cut " mixture which contains a smaller percentage of heroin but readily adheres to the tip of the cigarette.

Although all the addicts included in this study employed one of the methods described above, other procedures for the utilization of heroin were used by some of the individuals interviewed. " Red pills " (" hung yuen "), containing a relatively small quantity of heroin together with a variety of other ingredients, are smoked or, quite rarely, taken orally. Occasionally one encounters an addict who injects heroin intramuscularly or subcutaneously. The relatively slow absorption occurring with oral, subcutaneous or intramuscular administration of heroin makes these methods less popular than intravenous injection or the inhalation of heroin fumes.

Following selection, the patients were hospitalized and given bed rest, routine diet and water *ad libitum*. A quantitative estimate of the abstinence syndrome was made by grading the severity of the withdrawal signs and symptoms as absent (0), minimal (+, –), mild (+), moderate (++), severe (+++) or very severe (++++). Two points were given for each " plus " associated with " major " withdrawal symptoms — i.e., those symptoms which produce great discomfort; nausea, vomiting, diarrhoea, abdominal pain, anorexia, insomnia, twitchings and headache. Each " plus " associated with a " minor " complaint — i.e., increased perspiration, increased pilomotor activity, lacrimation, coryza, sneezing, hoarseness, dyspnoea and a feeling of cold, was assigned a value of one point each. Although the latter group of signs and symptoms are useful in evaluating the severity of the abstinence syndrome, they do not cause serious discomfort. Weakness, especially of the extremities, also represents a major complaint during the withdrawal period; however, this symptom was not included in the quantitative evaluation of the abstinence syndrome, since meprobamate itself, in the doses employed, produces weakness of the extremities (*vide infra*). Nocturnal seminal emissions may also cause the individual considerable concern. Their incidence, however, is relatively low, and this complaint, although noted, was therefore omitted from the quantitative evaluation.

Since withdrawal symptoms will abate merely with the passage of time, the effects of meprobamate administration were compared with those produced by the administration of placebos. Following the initial studies in which a suitable dose of meprobamate was determined, patients were selected at random to receive either meprobamate or placebo therapy. A " double blind " study — i.e., a study in which neither the evaluators nor the subjects are informed of the nature of the medication administered — was not employed owing to the lack of trained assistants and because those patients receiv-

[4] See *Bulletin on Narcotics*, vol. X, No. 3.

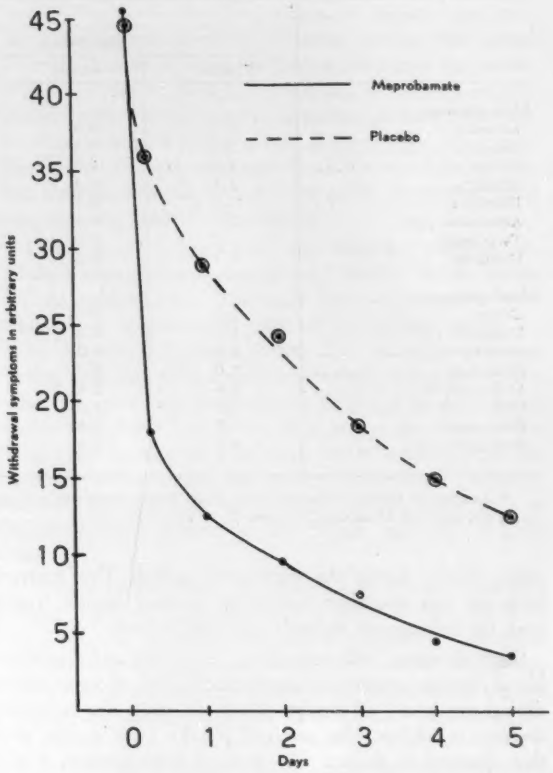
ing meprobamate therapy could be readily recognized, not only by the alleviation of their symptoms, but also by the changes in the tendon reflexes which occurred (*vide infra*). Drug therapy was initiated at approximately 10 a.m. on the day of selection and was continued at four-hour intervals (except for the 2 p.m. dosage) during the course of therapy, which normally lasted five days. Detailed analysis of the patients' response to therapy was made twice daily, at 10 a.m. and 4 p.m. Interim reports by hospital orderlies, warders and dressers were made at more frequent intervals.

Various doses of meprobamate were employed in the first ten patients, in an effort to determine the regimen which would produce the maximal relief of withdrawal symptoms without inducing significant side effects. As a precautionary measure against hypersensitivity, the initial dose was limited to 0.4 g. Subsequent administration of 1.6 g. every four hours produced dramatic alleviation of the withdrawal symptoms in several patients, but the maintainance of this dosage schedule caused one of these individuals to become semi-comatose within forty-eight hours after the initiation of therapy. Meprobamate administration was discontinued and twenty-four hours later this patient appeared relatively normal, but experienced a recurrence of his withdrawal symptoms. Maintenance doses of 0.4-0.8 g every four hours produced marked relief in several patients, but only slight to moderate relief in others. As a result of these initial studies, a regimen was selected which employed an initial dose of 0.4 g followed by a " priming " dose of 1.6 g and the subsequent administration of 1.2 g of meprobamate at four-hour intervals during the remainder of the five days of treatment. The 2 a.m. dosage was omitted if the patient was asleep. Fifteen addicts receiving this dosage were compared with a comparable group of fifteen patients who received placebos. Patients on placebo therapy received the same number of tablets which looked and tasted like the meprobamate tablets but contained inert substances. Unless otherwise noted, all numerical evaluations of results are based on these thirty patients.

Results

As shown in fig. 1, six hours after the initiation of therapy patients who had received meprobamate had approximately a 60% reduction in the severity of their abstinence syndrome. As would be expected, patients who received placebo therapy and its associated hospitalization and bed rest also had some alleviation of their complaints. The average percentage recovery in the placebo group at this time, however, was less than a quarter of that present in the meprobamate group. Five days of placebo therapy were required to produce a similar degree of recovery as that observed after one day of meprobamate treatment. When the severity of specific withdrawal symptoms is compared in the two groups (table 1) it is apparent that meprobamate markedly alleviates those abstinence symptoms associated with the gastro-intestinal and neuromuscular systems. Daily measurements of body weight were made in all subjetcs in an effort to obtain additional evidence of the relief of gastro-intestinal complaints.

Fig. 1. *Average severity of heroin withdrawal symptoms in patients receiving meprobamate or placebo therapy*



During the short period of hospitalization the maximum weight change which occurred in any patient under study was less than 6 lb. Nevertheless, the average weight gain in the meprobamate group was nearly twice that in the placebo group.

The effect of meprobamate on respiratory symptoms was less dramatic. During the period of treatment there was no significant difference in the incidence or severity of sneezing and hoarseness in the two groups. Coryza and " air hunger " were less intense in the group treated with meprobamate, but the degree of benefit was not marked. During the course of observation no significant variations in the resting respiratory rate were observed in patients who participated in this study. The severity of " air hunger ", which is experienced by most addicts during withdrawal, could not be closely correlated with changes in respiratory rate. This suggests that the shortness of breath is not due to abnormalities in pulmonary function, but rather involves higher brain centres.

Although headaches, when they occur, represent, from the standpoint of the patient, a serious withdrawal symptom, their incidence was not sufficiently great in either group to allow an evaluation of the effect of meprobamate on this symptom. It was likewise impossible to evaluate the effect of meprobamate on perspiration. Normally, increased perspi-

TABLE 1

Comparison of the effects of meprobamate and placebo therapy on the severity of heroin withdrawal symptoms

	AVERAGE SEVERITY OF SYMPTOMS *					
	Meprobamate			Placebo		
	Initial	6 hours	24 hours	Initial	6 hours	24 hours
Major symptoms						
Insomnia	3.2	0.9	0.4	3.1	3.1	2.8
Anorexia	2.8	1.3	0.8	2.4	2.0	1.7
Nausea	2.8	0.8	0.4	2.6	1.8	1.1
Vomiting	1.8	0.4	0.3	2.1	1.1	0.8
Diarrhoea	1.9	0.1	0.2	2.1	1.2	1.1
Abdominal pain	2.0	0.6	0.6	1.8	1.2	1.0
Twitchings	2.3	1.0	0.7	2.2	2.1	1.8
Headache	0.4	0.3	0.3	0.5	0.4	0.2
Minor symptoms						
Coryza	1.3	0.6	0.4	1.5	1.2	0.7
Dyspnoea	1.3	0.8	0.6	1.2	1.0	0.9
Sneezing	1.3	1.2	0.8	1.3	1.3	0.9
Hoarseness	1.0	0.8	0.7	1.0	0.9	0.8
Lachrymation	1.4	0.8	0.7	1.4	1.2	1.1
Chills	2.3	1.3	0.7	2.0	2.1	1.9
Pilomotion	1.2	0.6	0.2	1.0	0.9	0.7
Perspiration	1.8	1.6	1.3	1.7	1.6	1.4

* Average of fifteen subjects in each group before treatment and six and twenty-four hours after initiation of therapy. Symptoms graded as absent (0), mild (1), Moderate (2), severe (3) or very severe (4).

ration occurs during the withdrawal period. This study, however, was conducted during the summer months, and even the investigators themselves showed hyperhydrosis.

Slight decreases (5-20 mm of Hg) in systolic and diastolic blood pressures occurred in approximately 75% of the addicts during the course of therapy. However, since the average decrease in addicts who received placebos was similar to that observed in patients who received meprobamate, it is likely that the observed changes in blood pressure are due, in part at least, to hospitalization and bed rest and not to a specific drug action. Although Himmelsbach (1936) noted that a slight rise in blood pressure frequently occurs during the abstinence syndrome, all individuals included in this study had initial blood pressure readings within the range usually observed in non-addicts of comparable age and racial characteristics. It is possible, however, that the observed decreases in blood pressure during the course of therapy might be due in part to the waning of the abstinence syndrome.

The meprobamate regimen adopted after the initial trials produced relatively few side effects when it was employed in the treatment of the abstinence syndrome. Three addicts complained of slight dizziness forty-eight hours after the initiation of meprobamate therapy. Two of them also were mildly ataxic. These side effects, which were not severe enough to cause a cessation of drug therapy, subsided during the period of continued meprobamate administration. One individual who had been selected to participate in this study developed polyopia monopthalmica within twenty-four hours following the initial dose of meprobamate. Although it is not known whether this condition represents a bizarre withdrawal symptom or was due to meprobamate administration, it was deemed advisable to discontinue drug administration and to exclude this patient from further participation in the study. Normal vision returned approximately seventy-two hours later.

Most individuals who received meprobamate for the treatment of withdrawal symptoms showed mild evidence of somnolence. It is difficult, however, to estimate whether this increased tendency to sleep was the direct result of the sedative effect of the drug or was the normal bodily reaction to the elimination of the withdrawal symptoms, which in some cases had prevented sleep for more than forty-eight hours.

One patient on placebo therapy developed an acute psychotic state on the fourth day of hospitalization. During this period he attempted suicide and later became moderately violent. He had marked delusions of persecution and accused fellow inmates of attempted extortion and of causing all his relatives to be incarcerated. There was, of course, no substance in fact to these claims. An attempt was made to transfer this patient to meprobamate therapy, but he refused to swallow the tablets. Paraldehyde was therefore used to sedate this patient temporarily and he was subsequently transfered to a psychiatric hospital, where he recovered in approximately one week.

Similar psychotic states have been observed in other untreated individuals during the withdrawal period. From a scientific aspect it is fortunate that this patient had received placebos rather than meprobamate therapy. It is possible that meprobamate therapy might have prevented the development of this psychotic state; if, however, such a condition had occurred during the course of meprobamate therapy one might be prone to incriminate the drug as an agent which produces suicidal tendencies. In the light of this experience

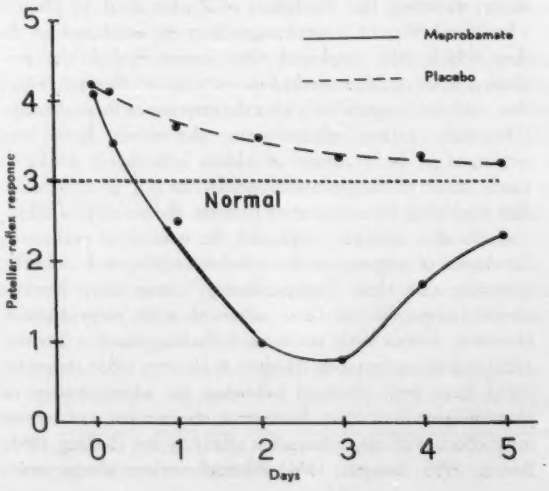
one must also wonder about the validity of statements which suggest that other tranquillizing drugs produce suicidal tendencies.

Four patients, not included in the numerical evaluation of the results, were treated with meprobamate because of convulsive states or fits which occurred during the withdrawal period. These individuals had clonic-tonic convulsions, with unconsciousness lasting from thirty to sixty minutes. Although these convulsions resemble to some extent those observed in *grand mal* epilepsy, these patients had no previous history of epilepsy. After the cessation of the initial convulsions these patients were given 1.2-1.6 g of meprobamate every four hours for periods up to five days. No further convulsions were observed in any of these patients. Although the relative infrequency and emergency nature of this condition prevented a controlled study employing placebos, previous experience indicates that these convulsive states usually recur frequently during the subsequent twenty-four hours even when barbiturates are employed as sedatives. The absence of additional convulsions following the administration of meprobamate gives additional suggestive evidence of the ability of this drug to alleviate withdrawal symptoms.

Two additional patients were treated with meprobamate because of acute psychotic symptoms attributed to narcotic withdrawal. Apparent recovery occurred within twenty-four hours following the administration of meprobamate. It is not possible, of course, to be certain that this drug therapy shortened the duration of these psychotic states; however, the psychotic symptoms which occur during drug withdrawal normally persist at least four or five days.

The patellar, achilles, biceps and triceps reflexes were tested in all patients receiving meprobamate or placebo therapy. Marked differences were noted between the tendon reflex responses in these two groups (fig. 2). Initially both groups had hyperactive tendon reflexes which were especially noticeable in the lower extremities. In the placebo group these reflexes gradually returned towards normal during the period of hospitalization. In contrast, reflexes were usually hypoactive twenty-four hours after the initiation of meprobamate therapy. Maximum depression of reflex activity was noted after 48-72 hours of treatment. During this period the patellar reflex could not be elicited in five of the fifteen meprobamate patients even when reinforcement techniques were employed. In four patients a response was obtained only when reinforcement techniques were used. In all but one of the remaining individuals in the meprobamate group the patellar reflex response was markedly diminished.

FIG. 2. *Comparison of the effect of meprobamate and placebo administration on the patellar reflex response during the heroin abstinence syndrome. Analysis of fifteen subjects in each group. Reflex response graded as absent (0), very sluggish (1), sluggish (2), normal (3), brisk (4), very brisk (5)*



Other stretch reflexes were also observed, although the changes were not as marked as those observed in the testing of the patellar reflex. The ankle jerk was absent or very sluggish in approximately 60% of the patients during the administration of meprobamate. The biceps and triceps reflex responses were usually sub-normal, but could still be elicited in all except three patients. In two of these the biceps reflex was absent, and in the third patient the triceps reflex could not be elicited. The depression of tendon reflex responses persisted during the course of meprobamate administration, although there was a slight tendency for reflexes to return towards normal on the fourth and fifth days of therapy.

Because of the ability of meprobamate therapy to depress reflex responses, it was thought possible that the failure of meprobamate to relieve the general weakness characteristic of the abstinence syndrome might be due to the substitution of a " drug-induced " weakness for that normally present during the withdrawal period. In an effort to substantiate this hypothesis, doses of meprobamate similar to those employed in addicts were administered to six normal volunteers. All of them developed marked weakness, dizziness and ataxia during the first twenty-four hours of drug administration. Meprobamate was discontinued at this time in two individuals who could no longer walk more than a few feet without support. The remaining four persons were able to tolerate these large doses of meprobamate for three days before it was necessary to discontinue this drug. The ankle and knee jerks were absent, and the biceps and triceps reflexes were markedly diminished in all these patients. Reflexes gradually returned to normal and the dizziness, weakness and ataxia disappeared within 72-96 hours following the cessation of meprobamate therapy.

COMMENT AND DISCUSSION

Although the method of analysis employed in this study clearly indicates the beneficial effects of meprobamate in the treatment of withdrawal symptoms, it probably minimizes the actual value of this drug in the therapy of the abstinence syndrome. During the withdrawal period addicts suffer severe " mental torture ". It is difficult to describe and perhaps impossible to quantitate this symptom. De Quincey, in his *Confessions of an English Opium Eater*, gives some indication of the nature of the mental suffering experienced by addicts. Although we were unable to obtain such adequate

descriptions from the subjects employed in this study, their remarks indicated that meprobamate therapy alleviated their mental distress. Most patients had experienced withdrawal symptoms several times previously during periods of incarceration. Subjects treated with meprobamate stated that " the suffering was much less than on previous occasions " and that " at other times the ' confusion ' lasted about ten days, while now it was gone in less than two days ". It is possible that mere hospitalization and bed rest contributed to the benefit which these patients received. However, patients on placebo therapy complained, " Why don't I feel better and why can't I sleep? The other people who are being treated have improved. What is wrong with me? " The patients on placebos, of course, did not know that they were being administered inactive tablets.

Although the use of a constant meprobamate regimen in the study facilitated the comparison of the effect of meprobamate and placebo therapy, it is recognized that a more flexible schedule would be advantageous when treating individual addicts. During the abstinence syndrome addicts show hyperactivity of the neuromuscular, gastro-intestinal and secretory systems. Meprobamate administration depresses these systems. The optimal dose of meprobamate, therefore, would be one which reduces the activity of these systems to normal, but does not produce hypofunction. The dose of meprobamate should therefore be graded in accordance with the severity of the withdrawal symptoms and the response of the individual to treatment. All patients selected for inclusion in this study had severe abstinence symptoms. Nevertheless, it is likely that those individuals who developed ataxia would have received significant relief with smaller doses of meprobamate. It is also probable that certain subjects, especially those who injected large doses of heroin intravenously, would have experienced more rapid improvement if larger doses of meprobamate had been employed. Unfortunaltey, there does not appear to be any simple criterion on which to base meprobamate dosage. Within limits, however, it appears that the continued presence of hyperactive tendon reflexes indicates inadequate dosage and the occurrence of ataxia and dizziness suggests supra-optimal dosage. It should be noted that the average weight of the patients included in this study is significantly less than might be expected in a comparable group in some other areas of the world. It is possible that even larger doses of meprobamate would be required to produce similar results in other racial groups who have a significantly larger stature.

The duration of treatment in this experiment was limited to five days, since the majority of the symptoms had disappeared during this period and because it was felt that longer periods of meprobamate therapy might result in meprobamate addiction (Lemere, 1956). One patient in the present study had *grand mal* type convulsions approximately twenty hours following abrupt meprobamate withdrawal. Although there were no sequelae following this convulsive episode, it would appear preferable gradually to decrease the dose administered over a period of several days in order to prevent the possibility of meprobamate withdrawal symptoms.

Adjunctive therapy was not employed in this study, because of the possibility that it might interfere with the evaluation of the effects of meprobamate. All the individuals selected for study were relatively healthy. Most addicts, however, have sub-standard diets, and it is likely that the anorexia which accompanies withdrawal produces further vitamin deficiencies which may contribute to a portion of the withdrawal symptoms, especially the generalized weakness. The concomitant administration of vitamin therapy should therefore prove beneficial in some cases. Other adjunctive therapy appears unnecessary in most cases, since adequate meprobamate dosage quickly relieves the withdrawal symptoms.

Although a direct comparison was not made with other methods employed in the treatment of heroin withdrawal symptoms, previous experience and an evaluation of published results indicate that meprobamate appears superior to other types of therapy utilized for this purpose. In general, most methods employ hospitalization with abrupt, rapid or gradual withdrawal of the narcotic with or without prior substitution therapy. Supplementary measures, including the use of sedatives, antispasmodics and anti-diarrhoeal agents, are employed to treat the specific symptoms which occur. Although controversy exists regarding the specific value of some of the agents employed in the symptomatic treatment of the withdrawal syndrome, it is apparent that many of these measures provide some degree of relief. With most of the regimens employed, however, significant withdrawal symptoms usually persist for several days to several weeks following the initiation of therapy. This is in marked contrast to the meprobamate therapy employed in this study which produced a dramatic reduction in the severity of withdrawal symptoms within six hours. Although Zucker, Machlin and Scott (1958) recently reported that " meprobamate is not of value as an adjunct in the management of the opiate withdrawal syndrome " the dose of meprobamate which they employed (1.6 g per day) was only approximately one-fourth of that which was selected in the present study. Our initial findings indicated that even 4 g per day of meprobamate may fail to provide adequate relief of the heroin abstinence syndrome. It is likely, therefore, that the failure of Zucker et al. to observe a beneficial effect of meprobamate may be attributed to the dose which they employed. One cannot exclude the possibility, however, that methadone substitution therapy, which they used, may significantly alter the response to meprobamate.

Recently various phenothiazine derivatives have been employed in the treatment of addicts (*vide supra*). Unfortunately most of the published results do not give sufficient data regarding the selection of patients, the severity of addiction, the dose schedule employed, the manner of evaluation, the degree of response or the controls employed. It is likely, however, that these " tranquillizing " drugs may produce results comparable to those observed with meprobamate. However, serious toxic reactions, including jaundice (Penber, 1955) and agranulocytosis (Hodges & Lazerte, 1955; Boleman, 1955), have been observed following the administration of phenothiazine derivatives. In contrast, the incidence of serious toxic effects with meprobamate is relatively low (Selling, 1955; Borrus, 1955; Lasagna, 1956) although various allergic reac-

tions have been observed (Borus, 1957). In view of the effectiveness and relative non-toxicity of meprobamate it appears that this agent may represent the drug of choice in the treatment of the abstinence syndrome.

All addicts employed in this experiment had been withdrawn from heroin for more than forty-six hours. Although this circumstance facilitated the selection of subjects for study, it precluded the testing of the ability of meprobamate to *prevent* withdrawal symptoms. It is felt likely that meprobamate would be effective in preventing abstinence symptoms in heroin addicts if the administration of suitable doses was initiated at the onset of withdrawal. Arrangements are contemplated which will allow the testing of this hypothesis.[5]

From a sociological standpoint, however, the complete prevention of abstinence symptoms might prove detrimental. Although previous reports indicate that the relapse rate among treated addicts is high (Vogel et al., 1948), the experience of withdrawal symptoms might act as a slight deterrent to the resumption of the use of narcotics. The present study has been conducted during a relatively brief period of time (three months) and it is as yet impossible to evaluate the effect of meprobamate treatment on the narcotic relapse rate. Many of the addicts who have been interviewed express an apparently sincere desire to break the habit (" kai tuen yuun "). There are, however, many factors which make it difficult for a former addict to abstain from the use of narcotics following his release from confinement. Many individuals return to their old environment and associates and are under considerable pressure to resume their old habits. Nevertheless, it is felt that in many cases hospitalization and treatment, even with placebos, will act as a definite deterrent to the resumption of narcotic usage. It is likely that if one believes he has received treatment for the " drug habit " this belief will act as a crutch which will, especially in borderline cases, strengthen the will power sufficiently to resist the temptation to resume the use of narcotics.

The marked inhibition of tendon reflexes produced in humans following the administration of large doses of meprobamate may represent a similar type of action of this drug on synaptic transmission as observed in animal experiments. Various investigators (Berger, 1954; Hendley et al., 1954) have shown that in cats meprobamate inhibits polysynaptic reflexes, such as the crossed extension reflex, but has an insignificant effect on monosynaptic reflexes, such as the patellar reflex. Unfortunately, no convenient method was available to test the effect of meprobamate on polysynaptic reflexes in humans. It is possible that the ataxia observed in some of the addicts and in normal volunteers may have been related to the inhibition of polysynaptic reflexes. However, the occurrence of diminished or absent patellar reflexes without evidence of ataxia perhaps suggests that in humans meprobamate has a greater tendency to affect monosynaptic reflexes than polysynaptic reflexes.

Since the physiological basis of withdrawal symptoms is unknown, it is impossible to reach any definite conclusions regarding the mechanism of action of meprobamate in the treatment of withdrawal symptoms. Tatum et al. (1929) and Seevers & Woods (1953) have suggested that the withdrawal symptoms might be due to the persistence of the stimulating effects of narcotics after the depressant effects have worn off. This theory has been criticized on the basis that certain drugs, such as the barbiturates, which have no significant stimulating action, may also produce withdrawal symptoms. The stimulatory effects, however, may not necessarily be due to the direct action of the drug, but rather to various bodily compensatory mechanisms which tend to counteract the depressant effects of the drug. Compensatory adjustments occur frequently following the administration of drugs. These are perhaps most often associated with the use of hormones, where the mechanisms of compensatory action are relatively well understood. They also occur with drugs which alter the blood pressure. Reflex bradycardia and vasodilatation may follow the administration of hypertensive agents. In many cases the compensatory mechanisms persist for a considerable time following the withdrawal of the initial stimulus. Thus hypothyroidism is frequently observed following the cessation of thyroxine therapy. Hypotension may result following the stoppage of adrenaline or noradrenaline infusions. It is possible that the compensatory mechanisms may account, in part at least, for the tolerance which occurs with continued administration of narcotics, and the persistence of compensatory readjustment after the termination of the direct effect of the drug might be responsible for the occurrence of withdrawal symptoms.

Unfortunately the mechanisms, if they do in fact exist, involved in the production of compensatory readjustments following the administration of narcotics are unknown. It is tempting to theorize that they involve facilitation of synaptic transmission and that meprobamate is effective because it alters synaptic transmission (Berger, 1954). Although the effect of meprobamate on synaptic transmission in the spinal cord may play a significant role in decreasing twitchings, the relatively uniform suppression of many of the withdrawal signs and symptoms by meprobamate indicates that it must also involve other areas of the central nervous system. The relatively selective effect on meprobamate of the electrical activity of the ventrolateral nucleus of the thalamus, reported by Hendley et al. (1954), suggests that this area might be primarily involved in the action of meprobamate. However, doses of meprobamate comparable to those employed in the present study also produce electro-encephalographic changes in other areas of the brain resembling those obtained after the administration of secobarbitone, phenobarbitone or paraldehyde (Pfeiffer et al., 1957). The effect of meprobamate cannot be explained merely on the basis of its sedative action, because sub-hypnotic doses of barbiturates fail to produce significant relief of many symptoms, especially those involving the gastro-intestinal tract, which occur during withdrawal.

Summary and conclusions

1. The administration of large doses of meprobamate to fifteen hospitalized heroin addicts suffering severe withdrawal

[5] Preliminary studies now being conducted indicate that meprobamate is capable of preventing many of the abstinence signs and symptoms in heroin addicts undergoing withdrawal.

symptoms decreased the average severity of the abstinence signs and symptoms more than 60% within six hours. At the end of five days of meprobamate therapy the withdrawal symptoms had decreased to less than 10% of the initial values. Significantly less improvement occurred in a comparable group of addicts who received placebos.

2. The administration of large doses of meprobamate to normal volunteers produced marked vertigo, ataxia and weakness. Vertigo and slight ataxia was observed in approximately 20% of the addicts who received meprobamate therapy.

3. Meprobamate produced marked inhibition of the patellar, achilles, biceps and triceps reflexes in both addicts and normal individuals.

4. It appears likely that meprobamate represents the drug of choice in the treatment of the heroin abstinence syndrome.

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Narcotic withdrawal symptoms in newborn infants

by Dr. Ralph H. Kunstadter, M.D.

With the alarming increase in the use of narcotics among young adults we are confronted with the serious problem of the care of infants born of narcotic-addicted mothers. Many of these infants are prematurely born, and the mortality is high. These infants are predisposed to asphyxia and anoxia and often have respiratory distress at birth or shortly thereafter. In addition to the more immediate serious effects of the narcotic on the infants during labour and shortly after birth, there may be symptoms and signs of narcotic withdrawal in those born of addicted mothers. These usually become manifest within hours after birth and if they are unrecognized and are not treated early, the infant may die.

Many of these mothers have had little or no prenatal care, and often little information is available when the infant arrives in the hospital. Therefore it becomes incumbent upon nurses and physicians to be aware of this potential hazard and to be able to recognize these infants, who present, in many instances, a classic syndrome of narcotic withdrawal signs.

The important symptoms and signs in their order of importance as observed by us and others are as follows: respiratory distress, including rapid respirations, grunting, retractions, intermittent cyanosis, and periods of apnea; hyperactivity with trembling, twitching, or convulsions; shrill high-pitched cry; sucking of hands and fingers as though constantly hungry; vomiting; diarrheoa; hyperpyrexia; excessive weight loss; sneezing; diaphoresis; anorexia; yawning; and incomplete Moro reflex.

The symptoms may appear shortly after birth or be delayed several hours or more, probably depending on the time relationship of the mother's most recent injection of narcotic and/or the dose to the time of birth. It has been stated that withdrawal symptoms do not occur unless the mother has taken the drug constantly, the last dose being administered less than a week prior to the birth of the baby. In our original group [1] consisting of five infants, we were able to confirm that three mothers were taking heroin intravenously; one, both heroin and morphine; and one we presumed was taking heroin, but we had no verification. All were habitual users, and the known duration of addiction, as self-admitted, was three, one and a half, and fourteen years respectively. The duration of addiction by the other two is unknown.

Since publication of our article in the *Journal of the American Medical Association*,[2] two additional infants with narcotic withdrawal symptoms have been observed. The sixth case was a male Negro infant, birth weight 3,155 g, seen during October 1958. The mother has been addicted to heroin for four years and takes two to three intravenous injections daily. The last injection was self-administered two hours and a half prior to delivery; dose approximately 4 mg. The infant was born at home; severe anoxia was present at birth and he was resuscitated with difficulty. At eight hours he began to vomit (prior to feeding), and this continued subsequently during the second twenty-four hours after feedings. Convulsions occurred during the first twenty-four hours.

The essential findings on admission to the hospital at two days and a half of age were: hyperactivity, shrill cry and vigorous sucking reflex (sucking fists continuously), and jaundice. The Moro reflex was incomplete, and tremors were present. Phenobarbital was administered, 8 mg every six hours, and discontinued on the fifth day. Jaundice increased during the first five days and gradually disappeared by the time of discharge on the tenth hospital day. A thorough haematologic study and liver function test indicated a mild hepatitis, toxic or infectious in origin, probably transmitted from an infected mother. The infant made a complete recovery.

A seventh case was born at Michael Reese Hospital on 30 November 1958, a white female infant weighing 2,757 g. The mother was twenty-five years of age, Para II, Gravida II, addicted to heroin for several years. Her first child had withdrawal symptoms and recovered after sixteen days in a hospital. She had been taking approximately 4 mg of heroin intravenously three to four times daily for several months. Her last injection was two hours prior to admission to the hospital, about six hours before delivery. There was some delay in onset of respiration, but no severe respiratory distress. Twelve hours after birth there were shrill cries, constant sucking of the fists and marked irritability. The Moro reflex was good. During the second twenty-four hours, the irritability became more marked, and intermittent quivering was present. There was no vomiting. Sodium luminal, 8 mg, was administered intramuscularly every six hours for two days. Symptoms gradually subsided by the sixth day and the infant was discharged to a foster home on the eighth day weighing 2,517 g.

The almost constant sucking and chewing on the hands and fingers as if hungry are rather dramatic and, we believe, unique signs, particularly in the premature baby. Vomiting and diarrhoea are frequent, and may be the only signs in the absence of the more typical nervous system manifestation. Respiratory distress is frequent, appears early, and may be manifested by cyanosis and rapid grunting respirations with or without retractions. The latter is highly suggestive of hyaline membrane disease, particularly when associated with periods of apnoea or rapid respiratory rate. Mortality is definitely related to the severity of respiratory distress, which in turn is partly dependent on the degree of intrauterine anoxia resulting from narcotization in utero. Proper treatment consists of the administration of sedatives, preferably diminishing doses of barbiturates, oxygen and antibiotics for respiratory distress, and fluid and electrolytes parenterally when indicated in the presence of vomiting, diarrhoea, and/or dehydration.

[1] As reported in *Journal of the American Medical Association*, *168*, 8, 25 October 1958. "Clinical notes : Narcotic withdrawal symptoms in newborn infants."

[2] See footnote 1.

Peyotl

*The peyotl is a cactus which grows in certain parts of Mexico and is used by various groups or tribes of Indians in Mexico and the United States for different purposes, including cult purposes. Its principal alkaloid, mescaline, is of some importance in psycho-pharmacology. Peyotl is not one of the drugs placed under international control by virtue of the international instruments relating to narcotic drugs. It was discussed at the twenty-first session of the League of Nations Advisory Committee on Traffic in Opium and Other Dangerous Drugs. The information in this article has been compiled from the literature published on the subject.**

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Historical Background

Peyotl has been known and used in the mountainous region of northern Mexico, which seems to be its habitat, from time immemorial; it was certainly in use in the pre-Colombian epoch and was probably used by the Chichimec tribe long before the Christian era.[1] The question of why it came into use originally is obviously insoluble, but at first there seems to have been no mystery about it, for any plant with a high water content is welcome in the arid region where it grows.

Indian legends attribute a divine origin to peyotl, and several variants of the manna myth are found, as well as magical myths, some of them linking the plant to certain animals: this symbolism reappears in various aspects of the peyotl cult.

The earliest historical references to it appear in the work of Spanish writers contemporary with the conquest of Mexico.[2] At that time missionaries and administrators tried to suppress peyotl consumption, for several reasons — *social:* they regarded it as an intoxicating substance dangerous to the individual and to society; *political:* they attributed to its consumption resistance to fatigue and hunger and the courage of certain tribes which they had difficulty in subduing; *religious:* they considered the use of peyotl to be a pagan practice, especially pernicious when it survived among Christianized Indians.

During the seventeenth and eighteenth centuries, peyotl was used in a vast area streching from the (present) state of Jalisco in Mexico to the Arkansas River. A true peyotl cult cannot be said to have existed at the time, but peyotl was used for two purposes: by *individuals*, as a medicine and to induce visions leading to prophetic utterance (this is a characteristic common to most sacred herbs, wherever found); and *collectively*, to obtain the desired state of trance for ritual dances. It should be observed, however, that the Indians were not the only ones who used peyotl at that period, for other sections of the population took to it, first the whites (and the Inquisition often intervened), then the Africans imported as slaves.

In the nineteenth century, considerable movements of Indian tribes occurred on each side of the Rio Grande,[3] although their chronology and even their interconnexion cannot be exactly determined: there were migrations northwards, but also raids from north to south (the largest seem to have been by the Kiowas, who got as far as southern Mexico towards the middle of the century). The ritual use of peyotl appears to have gradually become more fully organized, cult groups thus being established. Various authors, in particular Mooney,[4] Rouhier[5] and Slotkin,[6] have tried to trace the progress of the activities which finally led to the establishment of the peyotl church at the end of the nineteenth century. They have not been completely successful, but they supply useful signposts. Broadly speaking, it may be said that the rite, moving up from Mexico, was adopted by the Mescalero-Apaches of New Mexico, who passed it on to the Comanches and Kiowas (1840). Later, it spread to the Tonkawas and Kickapoos (1860), then to the Wichitas, Cheyennes, Arapahos and Omahas and, finally, about 1910, to the Osages.

A general census of peyotl votaries has been compiled by Rouhier[7] on the basis of documentation supplied by the Bureau of Indian Affairs at Washington. What is noteworthy is, first, the small number of votaries (a few thousand) and, secondly, the wide dispersion of the cult, which — apart from four Indian tribes in Mexico — spread to some forty Indian tribes in the United States living in ten different states.

* At the end of this article will be found a bibliography. All references given as " op. cit. " are to works listed therein.

[1] B. de Sahagun, op. cit.

[2] For the literature dealing with peyotism in the sixteenth and seventeenth centuries, see especially J. S. Slotkin: *Peyotism, 1521–1891*, op. cit.

[3] The Rio Grande del Norte, which at present forms the frontier between Texas and Mexico along most of its course.

[4] J. Mooney: op. cit., passim; the bibliography lists only one of his works (for reasons of space). A list will be found in Slotkin (see footnote 6).

[5] A Rouhier: *Le Peyotl*, op. cit.

[6] J. S. Slotkin: *Peyotism, 1521-1891*, op. cit.

[7] See footnote 5.

FIG. 1. — **Two aspects of a peyotl in flower**

FIG. 1 *a*

FIG. 1 *b*

Photos communicated by Mr. A. Bertrand, Nogent-sur-Marne. (Copyright.)

The peyotl cult, which will be briefly studied below, was spread by Indians among Indians; the whites have never had any part in it. Incidentally, the Indians often behaved as genuine evangelists, risking the severities of the law in order to spread the cult.

It should be added that the cult was spread, not by " primitive " Indians, but, it would seem, rather by educated Indians — those re-entering the reservations — who tried to keep it alive when they returned from college or university. Since the publication of Rouhier's table the peyotl cult has been found among other tribes or groups: among the Delawares,[8] and even among negroes.[9]

* * *

The Native American Church was thus established in the United States, but to deal with it here would exceed the scope of this article and, in any case, it seems to be an ethnographical curiosity rather than an important movement. As has already been stated, attempts were made first by the Spanish colonizers and then by the Inquisition to suppress the use of peyotl, and they are still being made in certain states in the United States. Peyotl is not regarded as a narcotic drug, and its use is not prohibited by the Federal Government,[10] but it is prohibited in certain states. A Montana state law lays down that it is an offence to sell or supply peyotl in any manner whatsoever.[11] In 1926 an Indian, Big Sheep, was prosecuted and convicted under this law. (Big Sheep stated that he was a member of the Native American Church and that peyotl was used by the faithful of this church solely for ritual purposes in the adoration of God, according to the belief of the faithful, their interpretation of the Holy Bible and the dictates of their conscience.) Peyotl is also prohibited in California. In 1957, acting on information sent by the inspector at Laredo, the Californian state and district officers confiscated an express parcel containing 20 lb of peyotl.[12]

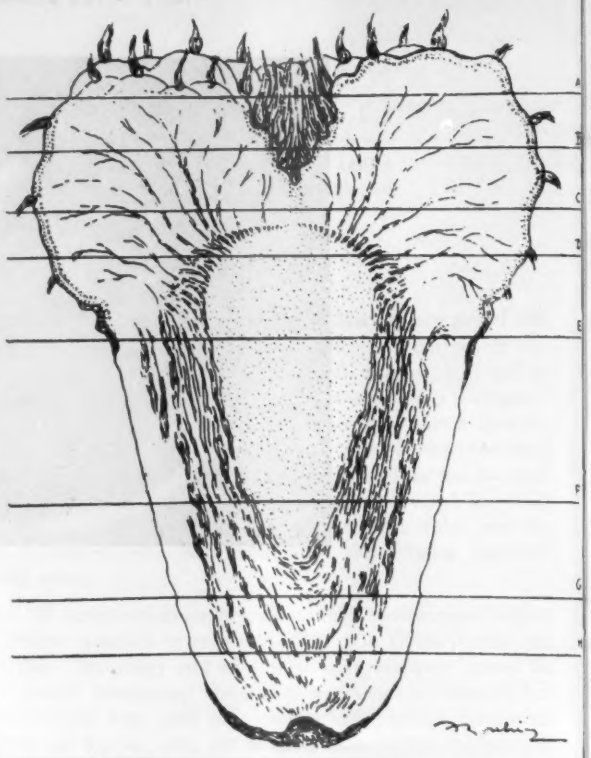
Lastly, it may be added — though it is only a trivial matter — that there was a " peyotl dispute " in the United States about 1950, and that certain ethnologists protested strongly against the idea that the use of peyotl should be prohibited, stating that the Native American Church is a legitimate religious organization with the same right to religious freedom as other churches.[13]

Description

The peyotl (*Echinocactus Williamsii Lems*) belongs to the cactus family, a sub-family of the echinocacti, genus *Echinocactus*, sub-genus *Lophophora* (this consists of only one species, the *Echinocactus Williamsii Lems*).

Rouhier (op. cit.) gives the following description of it: " The plant is small, simple or cespitose, proliferous, turbinate,

Fig. 2. — **Longitudinal section of peyotl**



A, B, C, D: spherical portion; E: collar into which the epidermis disappear F: underground chlorophyllose stalk, part above ground where the sube begins; G, H: root.

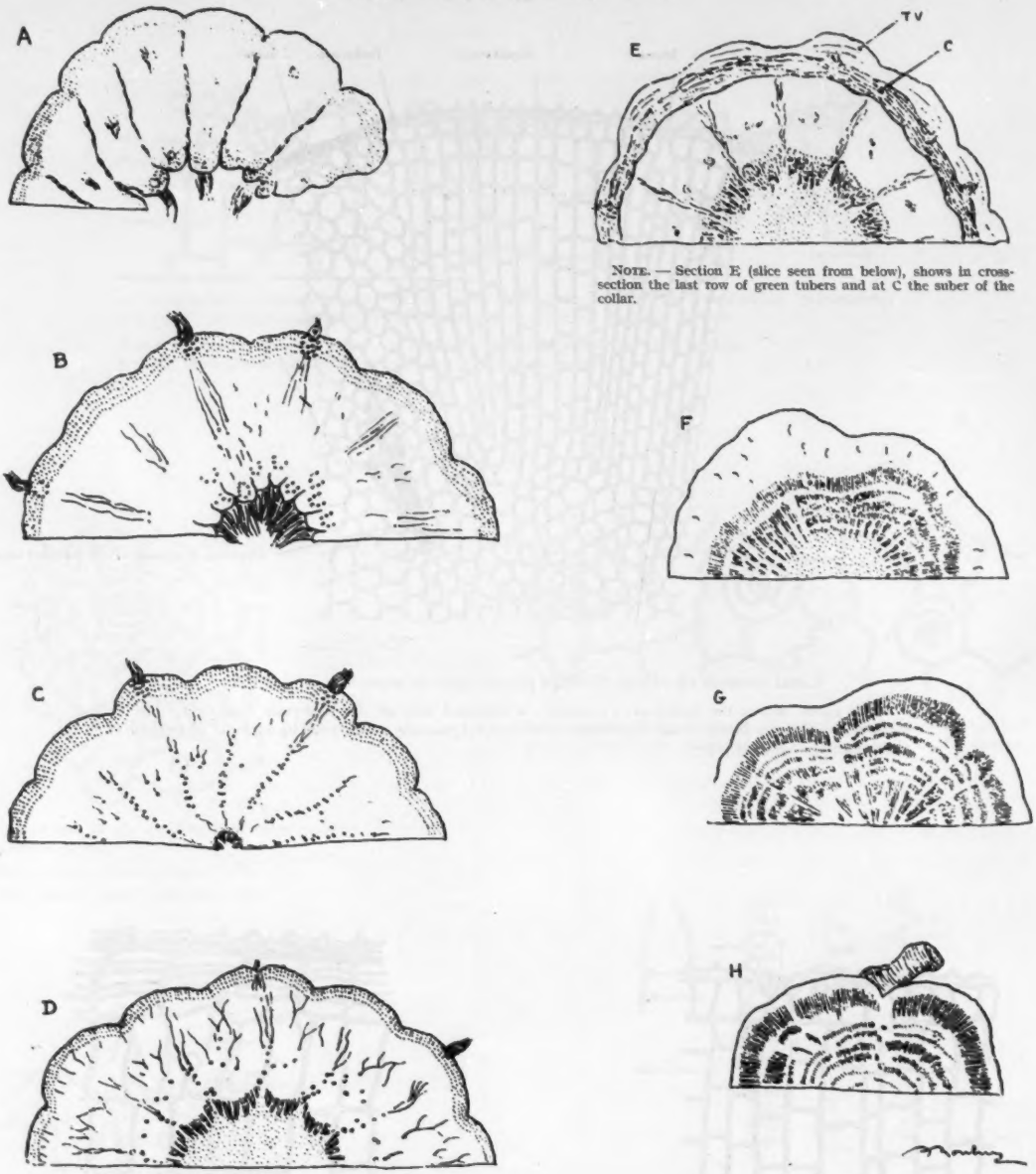
(This figure, together with figures 3, 4 and 5, is taken from the book by A. Rouhie *Le Peyotl*, Doin, Paris, 1927.)

with a thick, napiform root. The cylindrical stalk, which has horizontal wrinkles caused by the sinking of the tubers, is suberized and greyish-fawn in colour; at the end it becomes more chlorophyllose, globular, flattened and sage-green in colour; it is divided into five to thirteen thick ribs, only slightly salient, rounded, separated from each other by well-marked longitudinal straight or sinuous grooves. These ribs are divided by shallow transverse grooves, usually at right angles to the others, into broad, flattened, relatively polyhedral tubers bearing at the top a round, inerm areola with tufts of erect long white silky hairs. As the areolae of the young tubers draw closer, the markedly umbilicate centre of the plant grows a thick pad of silky hairs from which the flowers emerge. These flowers, pink or sometimes white or yellowish, are apiculate, solitary, small, infundibuliform, with a bare glabrous ovary. The fruit is a flesh-coloured, or sometimes greenish-yellow, berry, which contains a few small dull black seeds with a granulated epidermis."

The plant rarely exceeds 15 to 20 cm in total length. Much of the plant is underground (more than half the total length). The stalk is very short, the chlorophyllose portion being broad and globular. A curious feature is that it stores water during

[8] V. Petrullo: *The Diabolic Root*, op. cit.
[9] M. G. Smith: *Ethnology: A Negro Peyotl Cult*, op. cit.
[10] See J. S. Slotkin: *Menomini Peyotism*, op. cit.
[11] See W. R. Arthur: *The Law of Drugs and Druggists*, St. Paul West Publishing Co., 1935.
[12] *Monthly Narcotics Intelligence Bulletin*, 15 September 1957 (Publication of the United States Treasury Department).
[13] *Science Newsletter*, 8 December 1951.

FIG. 3. — **Cross-sections of peyotl (made at the levels shown in figure 2)**



NOTE. — Section E (slice seen from below), shows in cross-section the last row of green tubers and at C the suber of the collar.

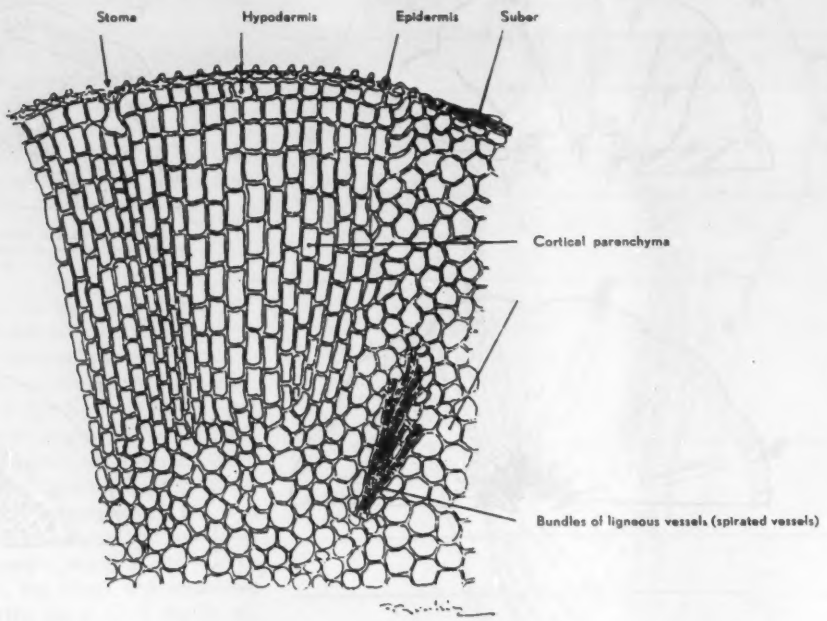
the rainy season, becoming swollen and plump, whereas drought shrivels it so much that it is hard to believe that it is the same plant. The plant flowers — in its normal habitat — after the rains — i.e., from May to July.

Figures 2 and 3 show longitudinal and cross-sections of the peyotl. The sections in figure 3 marked "A", "B", etc. correspond to the areas marked with the same letters in the longitudinal section in figure 2.

Figures 4 and 5 show the histological characteristics of the peyotl stalk. It should be noted that many of the cells of the cortical parenchyma "contain crystals of oxalate of lime in echini or elongated masses. They are sometimes literally stuffed with them and they appear in large numbers, especially in mature peyotls or peyotls straight from Mexico."[15]

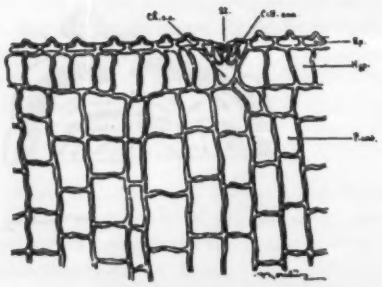
[15] A. Rouhier: *Le Peyotl*, op. cit.

FIG. 4. — **Histology of peyotl (stalk)**



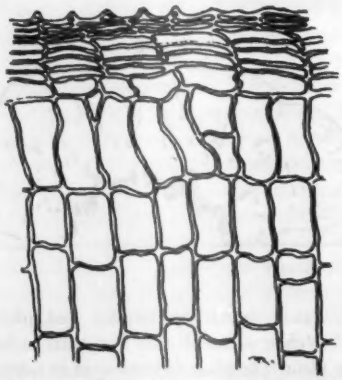
Radial section of rib of large 12-ribbed peyotl (upper chlorophyllose area of stalk).

This figure shows: the epidermis — a stoma — a sunerized area of the epidermis (top right), probably the result of a bruise — the hypodermis — the cortical parenchyma traversed by a bundle of spirated vessels leading to the periphery.



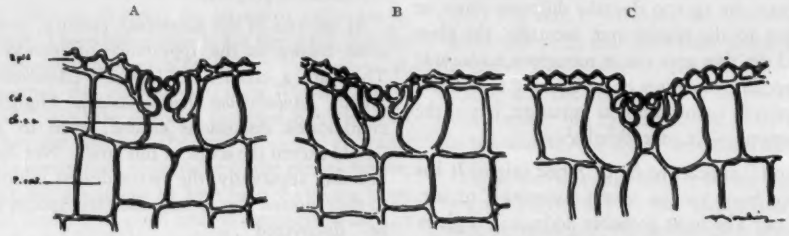
Radial section of rib of large 12-ribbed peyotl.

Cell. ann.	— Appendent cells
St.	= Stoma
Ch. s. s.	= Sub-stomatic space
Ep.	= Epidermis
Hyp.	= Hypodermis
P. cort.	= Cortical parenchyma



Radial section of rib of large 12-ribbed peyotl showing a portion of the epidermis in course of suberization.

FIG. 5. — **Histology of peyotl (stalk)**



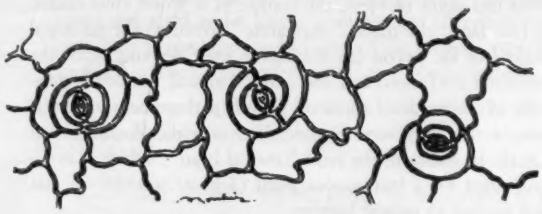
Longitudinal sections of three different ribs of the same 8-ribbed peyotl showing characteristics regarded by Michaelis as specifically differentiating *Ech. Williamsii* from *Ech. Lewinii*.

A and B show a numerical difference between the appendent cells of their stomata.
B and C show different forms of the epidermic papillose projections.

Cross-section of the epidermis of large 12-ribbed peyotl.

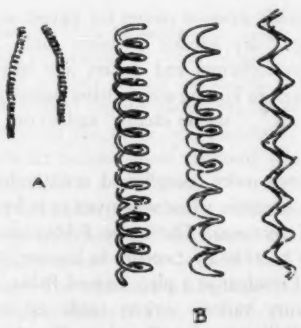
Above, stoma with 4 appendent cells.

Below, stoma with 2 appendent cells.



Cross-section of the epidermis of young lateral shoot of 8-ribbed peyotl, showing the ostiola and the appendent cells of the stomata.

Epidermis of 8-ribbed peyotl seen from above (in perspective) and showing papillose projections of the cells.



A, spirated vessels slightly enlarged.
B, various aspects of the spirated vessels.

The longitudinal sections above come from the same peyotl; but there is not the same number of appendent cells of the stomata, so that this number does not constitute a characteristic differentiating *Echinocactus Williamsii Lem* from *Echinocactus Lewinii*, as has sometimes been asserted.[16]

[16] P. Michaelis: *Beiträge* ..., op. cit.

Terminology and Taxonomy

The terminological difficulties which arise in dealing with peyotl are of a twofold nature; to begin with, this term has been used throughout the ages to describe different plants or substances according to the region and, secondly, the plant is polymorphic and can thus give rise to numerous taxonomic interpretations, especially when it is borne in mind that it was studied in the nineteenth century, not as in nature, but in the form of mescal buttons — i.e., the dried slice.

The word " peyotl " appears to be of Aztec origin. It has been said to derive from various words meaning " to stir, stimulate " and so on. The most probable derivation is given by Molina[17] in his dictionary — namely, that it comes from Nahuatl " peyutl ", which means something white and silky, like a cocoon, an apt description of the fresh peyotl because of the tuft of silky hairs crowning it. But this word has always had a generic sense with different meanings. A list is given by J. S. Slotkin.[18] Moreover, there is some confusion with " mescal ", which is itself a generic term designating a cactus as well as the food and fermented beverages obtained from it. From this point of view, the confusion is worse confounded by two facts: the name " mescaline " given to the principal alkaloid of the peyotl (an attribution itself deriving from the prevailing confusion) and the name " mescal buttons ", generally given to dried slices of peyotl (perhaps because it was thought that they were intoxicating, as is the alcohol called mescal). In addition, the term " mescal bean ", which is ordinarily used for a leguminous plant (*Sophora secundiflora*), has been applied to mescal buttons.

The word " peyotl " is generally accepted throughout Mexico, though there are special terms for peyotl in the various tribal languages : " nicouri " among the Huichols of Jalisco and the Tarahumares of Chihuahua, " kamaba " among the Tepehuanes of Durango, " wokowi " among the Comanches, and so on.[19]

Lastly, two other series of names for peyotl are found: in traffickers' slang: " dry whisky ", " white mule ", and in the jargon of cactus collectors and dealers (the latter of course have every interest in putting out as many names as possible): " dumpling cactus ", " turnip cactus " and so on, referring to its shape.

Things are even more complicated taxonomically. Historically, the first scientific name was given to it by Hernández in 1638: *Peyotl zacatensis*. The name *Echinocactus Williamsii* was given to it in 1840 by Lemaire in honour of Williams, a British official resident at a place named Bahia. During the nineteenth century various writers made up other names (*Anhalonium Williamsii*, by Engelman,[20] *Ariocarpus*, by Scheidweiller, and so on). In 1894, Coulter created the genus *Lophophora* for the peyotl and called it *Lophophora Williamsii*, a name which some authors still keep.[21] Finally, in 1889, Schumann put peyotl back into the echinocactus genus and made of the *Echinocactus Williamsii* the single species of the sub-genus *Lophophora*.[22]

At the end of the nineteenth century, however, difficulties arose owing to the appearance of pseudo " new species ". These are a creation of Lewin[23] (*Anhalonium Lewinii*) and Rebut (*Anhalonium Jourdanianum*). Highly confused and complicated discussions ensued; even to summarize them would exceed the scope of this article. Not only the botanists, but also, apparently, the cactus dealers joined in, since it was to their interest that as many different species as possible should be " discovered ".

The conclusion to be drawn from the literature consulted would seem to be that the different types of peyotl belong to a single species, the confusion arising from the differences between the young peyotl, with about eight straight ribs, and the mature peyotl, with about twelve sinuous ribs; the third form, with irregular ribs, may derive from one or other of those forms, and the three forms may be found on a single root.

The designation *Echinocactus Williamsii*, which is to be found in the *Kew Index* (Vol. II, p. 813), has been adopted in this article, it being understood that the designation *Lophophora Williamsii* might also be used.

Habitat and Gathering

The peyotl grows wild on the Mexican plateau and in the southern part of Texas along the Rio Grande. It is to be found in the following Mexican states: Chihuahua, Coahuila, Nuevo Leon, Tamaulipas, Zacatecas, San Luis Potosi, Queretaro, Hidalgo and Sonora.[24] These regions are fairly high (1,800 to 2,000 metres), and have a very long dry season, with some rains in summer. The soil is in general calcareous. The peyotl grows in dry places, on cliffs or rocky slopes. These regions are very hot and the vegetation is sub-tropical.

The peyotl grows at ground level, sometimes singly, more often in clusters. It is barely visible, except when it is in flower, since it is usually more or less covered over with earth and looks like a pebble. It is very common in certain places, which often take their names from it (the village of Hicori in Sonora, Peyotan in Jalisco, etc.).

It should be added that the peyotl can be cultivated anywhere under glass or in a room, as many cactus fanciers know. It does not seem to be unduly susceptible to cold, for Rouhier[25] says that certain specimens survived during the 1914-1918 war in a greenhouse in which the temperature fell to 2° C. (A similar observation comes from the curator of the Geneva Botanical Gardens.)

* * *

[17] Molina (Fray Alonso de: *Vocabulario en lengua castellana y mexicana*, Mexico 1571).

[18] J. S. Slotkin: *Peyotism, 1521–1891*, op. cit.

[19] These terms are phonetic spellings of unwritten Indian terms and may therefore be spelled differently by different authors. The same applies to the word " peyotl " when it passes into non-Indian languages.

[20] Engelman: *Synopsis of* . . . , op. cit.

[21] Coulter : *Preliminary revision* . . . , op. cit.

[22] K. Schumann : *Gesamtbeschreibung der Kakteen*, op. cit.

[23] L. Lewin : *Uber Anhalonium Lewinii*, op. cit.

[24] According to a pamphlet published by the *Instituto Médico Nacional de México* (1913), quoted by A. Rouhier, *Le Peyotl*, op. cit

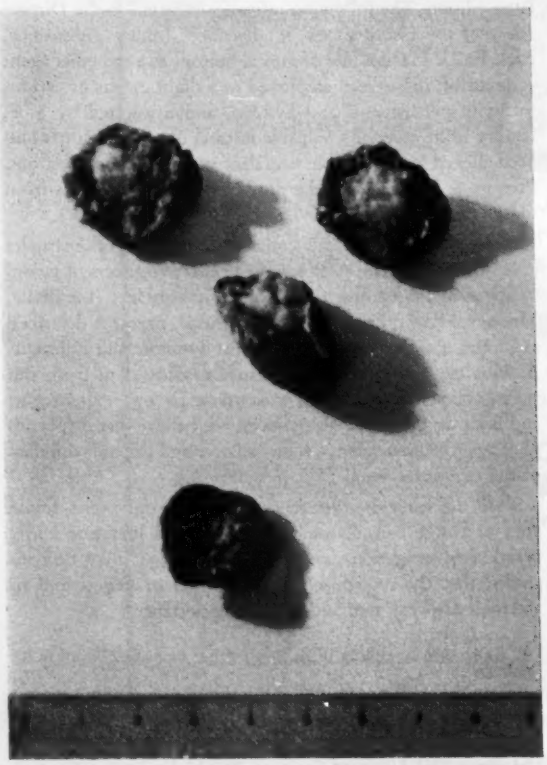
[25] A. Rouhier, *Le Peyotl*, op. cit.

Peyotl gathering may be regarded in two different ways, according to the use to be made of the plant; (1) gathering for direct consumption — i.e., by the Mexican Indians for themselves, and (2) gathering for sale. In the first case there is sometimes a religious element; the second is gathering in the ordinary sense. The whole cactus is not uprooted, but the part of the plant above ground is lopped off by machete. If this part is too large, it is cut into two slices. These slices are green and usually juicy (the peyotl is gathered after the rains if possible). They are dried in the sun, become dehydrated and assume the characteristic appearance of the mescal button, a form in which the peyotl can be kept for a very long time. It is in this form that it is supplied both to members of the cult and to those who buy it for non-religious purposes, and it is mainly in this form that it is found at druggists' and in *materia medica*. This makes fraudulent imitations easier, for it is very hard to distinguish at first sight a genuine mescal button from a dried slice of some other cactus.

In a bundle of mescal buttons (which are gathered by hand, not mechanically, and so show any number of irregularities) most of them are upper slices: single slices of small peyotls, No. 1 slices of large peyotls, together with a varying proportion of lower slices.

The upper slices vary in shape, being usually disc-like, brown or grey in colour, with the edges turned upwards.

FIG. 6. — **Mescal buttons, upper slices**



(Scale in cm) (Uncertain origin)

The diameter varies between 2 and 4 cm; thickness from 10 to 20 mm. The surface corresponding to the top of the plant has the tuft of greyish-white apicular hairs in the middle. Fragments of flowers or dried fruits may be found among them. The skin is wrinkled, the ribs salient. The areolae are visible and often still have their hairs. The under surface of the upper slice is slightly conical, with wrinkles more prominent near the centre. Not infrequently there is an orifice in the centre; this means that the section has been taken near the top and has cut across the central infundibulum.

The lower slices are similar to the upper ones, except that they are larger, have no ribs, and of course no tuft or apicular hairs. Furthermore, the epidermis is better marked and forms a kind of rim to the rest of the slice, which is very thin (1 to 3 mm). Since they are so thin, the lower slices readily lose their shape and assume even more irregular forms than the others.

The mescal button seems at first sight hard to use. It looks like a dried mushroom and swells very rapidly in boiling water, slowly in cold water. It soon softens in the mouth and can then be chewed, the flesh seeming elastic. The taste is bitter and acrid, and it leaves an unpleasant after-taste accompanied by slight burns and itching of the mucous membrane. Its smell is sharp and nauseating when it is rehydrated.

To work on the mescal button it must either be ground, if it is still fresh (it is then elastic), or be cut up or pounded in a mortar.

It is feasible, though difficult, owing to dessication, to establish the identity of a mescal button by microscopic examination; all the vessels are contracted and distorted, but the areola hairs, the spirated vessels, the parenchyma cells (see figs. 4 and 5) and the oxalate of lime crystals agglomerated in echini can be distinguished.

Chemical Aspects

The first attempts to isolate the active principle of peyotl were made by Lewin [26] in 1888. Working on mescal buttons, he isolated a body which he called anhalonine. In 1894 Heffter [26] worked on live plants. He isolated another alkaloid which received the name of pellotine or peyotine. Shortly afterwards he isolated three alkaloids which he called A, B and C. Alkaloid A was mescaline. In 1896 Heffter completely separated mescaline, anhalonine, anhalonidine, and lophophorine. In 1899 Kayder [26] discovered another alkaloid in the mescal buttons on which he was working and named it anhalamine. The method has long been used by those desirous of studying the effects of these alkaloids. It is still used, although it is true that practically all the mescaline used throughout the world is synthetic.

In 1919, E. Späth [26] resumed the research and succeeded in synthesizing the alkaloids of the peyotl. His work is of the utmost importance, as it has shown that the peyotl alkaloids can be divided into three groups, very close to each other, but with individual structures:

[26] See bibliography for his main works on the subject.

Group 1

Mescaline: $C_{11}H_{17}NO_3$

Group 2

Anhalamine: $C_{11}H_{15}NO_3$
Anhalonidine: $C^{12}H^{17}NO_3$
Peyotine: $C_{13}H_{19}NO_3$

Group 3

Anhalonine: $C_{12}H_{15}NO_3$
Lophophorine: $C_{13}H_{17}NO_3$

The figures given in the literature for the percentage of alkaloids in the plant seem to be neither very accurate nor readily comparable. Some percentages found by Rouhier [27] may be given by way of example: weight in percentage of total alkaloids in upper slices of mescal buttons, 3.70; lower slices, 3.43; dried peyotl heads, 3.14; roots, 0.73; fresh peyotl heads (moisture content 82.5%), 0.41; fresh peyotl roots (moisture content 75.2%), 0.244.

The following conclusions emerge from the literature with regard to the aggregate alkaloids. They are all found in the mescal buttons; the alkaloid content changes with the conditions of vegetation, the time of gathering, and the nature of the soil in which the plants grow. The alkaloid content of mescal buttons diminishes with time.

* * *

The physical and chemical properties of the alkaloids of the peyotl are as follows: [28]

Mescaline. 3, 4, 5-trimethoxyphenethylamine. Molecular weight 211.25. Carbon 62.54%, hydrogen 8.11%, nitrogen 6.33%. Crystals, melting point 35-36°. Moderately soluble in water; soluble in alcohol, chloroform, benzine; almost insoluble in ether.

Anhalamine. 7, 8-dimethoxy-6-hydroxy-1, 2, 3, 4-tetrahydroisoquinoline. Molecular weight 209.24. Carbon 63.14%, hydrogen 7.25%, nitrogen 6.29%. Crystals, melting point 187-188°. Almost insoluble in cold water, cold alcohol or ether; soluble in hot water, alcohol and acetone. (Now believed to be 6, 7-dimethoxy-8-hydroxy-1, 2, 3, 4-tetrahydroisoquinoline).

Anhalonidine. 7, 8-dimethoxy-8-hydroxy-1-methyl-1, 2, 3, 4-tetrahydroisoquinoline. Molecular weight 223.24. Carbon 64.55%, hydrogen 7.68%, nitrogen 6.27%. Needles, melting point 100°. Optically inactive. Salts are dextrogyrate. Soluble in water, alcohol, chloroform; slightly in ether.

Peyotine.[29] 8-hydroxy-6, 7-dimethoxy-1, 2-dimethyl-1, 2, 3, 4-tetrahydroisoquinoline. Molecular weight 237.29. Carbon 65.80%, hydrogen 8.07%, nitrogen 5.90%, Melting point close to 111.5°. Optically inactive. Freely soluble in alcohol, ether, acetone, chloroform, benzine; sparingly soluble in cold petrol ether and cold water; more soluble in boiling water.

Anhalonine. 8-methoxy-6, 7-methylenidioxy-1-methyltetrahydroisoquinoline.[30] Molecular weight 221.25. Carbon 65.14%, hydrogen 6.83%, nitrogen 6.33%. Very soluble in alcohol, ether, chloroform, benzine, petrol ether. Freely soluble in hot water.

Lophophorine.[31] N-Methylanhalonine. Molecular weight 235.25. Carbon 66.36%, hydrogen 7.28%, nitrogen 5.95%. Soluble in ether, chloroform.

Effects and Uses of Peyotl and its Alkaloids

Mescal buttons are easily adaptable for galenical preparations such as powders, extracts, tinctures and the like. Rouhier [32] mentions the following preparations, giving the dosage and method of preparation. Powder: 1/5 tincture of peyotl; fluid extract, weight for weight of peyotl; fluid acid extract, weight for weight of peyotl; soft hydro-alcoholic extract of peyotl; soft chloroformic extract of peyotl; totum of the hydrochlorates of peyotl alkaloids; alkaloid solution for injection, weight for weight of peyotl. None of these preparations has been found in the national pharmacopoeias consulted; in fact neither peyotl nor mescaline is mentioned in them. The pharmacopoeias of more than twenty countries, including France, Mexico, the United Kingdom and the United States of America have been consulted, usually in the latest edition. The following reference is found in the *Dispensatory of the United States of America* [33] (under *anhalonium*, page 1261): " The value of mescal buttons as a remedial agent is doubtful; it has been employed to a slight extent in various forms of neurasthenia and hysteria, and is asserted by S. F. Landry to be especially valuable in cases of asthma. It has also been alleged to be useful in neuralgic and rheumatic affections. Prentiss & Morgan give the dose of the fluid extract as from ten to fifteen minims (0.6-0.9 cc)."

However, the literature contains a number of examples given by non-Indian scientists of the curative effects of peyotl or its alkaloids on themselves or their assistants (Lumholtz, Mooney, Dixon, Landry, etc.). In general, peyotl is described as a tonic, a sedative, a remedy against dyspnoea and a diuretic. A. Rouhier,[34] who has made a special study of it from this point of view, concludes: " According to our experiments and until we gain wider experience, we believe that it (peyotl) may be recommended as a tonic sedative and general stimulant of the nervous system."

Since the foregoing references were the only ones found after extensive consultation of the technical literature and a practical investigation gave no other result, it may be concluded that the recognized remedial uses of peyotl and its alkaloids are very rare and of little importance.

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[27] A. Rouhier: *Le Peyotl*, op. cit.
[28] According to the *Merck Index of Chemicals and Drugs*, 6th edition, Merck & Co. Inc., Rahway, N.J. (United States of America).
[29] Called pellotine in the *Merck Index*.
[30] Name given according to A. Rouhier (see footnote 29); not in the *Merck Index*.
[31] The *Merck Index* spells it " Lophorphorine " (probably a printer's error).
[32] Op. cit.
[33] *Dispensatory of the United States of America*, by H. C. Wood & A. Osol, 23rd edition, 1943, Lippincott Company, Philadelphia, London, Montreal.
[34] Op. cit.

FIG. 7. — **Handbill for "Peyotyl"**

PEYOTYL
LE PEYOTYL
R. D.
Le "PEYOTYL R. D.", produit naturel n'ayant subi aucune transformation ou altération chimique conserve, vivantes, toutes les propriétés merveilleuses du Peyotl (Lophophora Williamsii).
Cette plante est connue et utilisée depuis des siècles par les Indiens du Mexique pour ses vertus thérapeutiques, à la fois toniques et sédatives qui en font l'un des meilleurs reconstituants naturels et l'arme la plus sûre contre la douleur. C'est également un antispasmodique remarquable et le spécifique, par excellence, de toutes les névroses.
Les recherches scientifiques les plus récentes permettent d'affirmer que le PEYOTYL R. D., substance même du Peyotl, n'a aucun effet intoxicant sur l'organisme et n'est contre-indiqué en aucun cas. Il diffère fondamentalement des excitants ou des calmants ordinaires, à l'effet d'ailleurs fugace, en ce que son emploi peut être prolongé sans trouble ni accoutumance.
Le "PEYOTYL R.D." pris régulièrement ramène l'équilibre et le calme et favorise un plein épanouissement des facultés de l'individu.
INDICATIONS : Asthénie, Convalescences, Surmenage physique et intellectuel, Dépression nerveuse, Neurasthénie, Insomnie, Migraines, Névralgies, Douleurs abdominales et rhumatismales, Asthme, Dyspnée, Hystérie, Toux d'irritation.
DOSE : 2 à 4 dragées par jour avant les repas.
Contre l'insomnie : 1 ou 2 dragées avant de se coucher, à une heure d'intervalle.
PAS D'ACCOUTUMANCE
Le Flacon de 20 dragées : en vente au prix imposé : 14 fr. 95, impôt
Une Brochure détaillée sur le Peyotl est envoyée sur simple demande

(Facsimile)

FIG. 8. — **Handbill, with testimonials for "Peyotyl"**

ATTESTATIONS De nombreuses personnes que le **PEYOTYL R. D.** a soulagées de leurs douleurs, ont bien voulu nous exprimer leur satisfaction.

Voici parmi tant d'autres, quelques attestations :

•

Paris, 8 février 1933.

Messieurs,

Sujet à de fréquents maux de tête, je suis heureux de vous faire connaître que j'ai trouvé, en prenant un cachet de Peyotyl, un soulagement beaucoup plus rapide et plus efficace qu'avec tout autre produit.

J'ai constaté, également, que les cachets pris le soir, avant de se coucher, procurent un repos parfait et un grand bien-être le lendemain.

Vous pouvez faire, de ma lettre, l'usage que bon vous semblera et, avec reconnaissance.

Je vous présente mes meilleures salutations

•

Brunoy, le 9 février 1933.

Messieurs,

Je vous fais savoir par la présente que je suis enchantée de vos cachets Peyotyl que j'ai employés pour mes maux de tête et maux de cœur et qui m'ont donné entière satisfaction.

Recevez, Messieurs, mes salutations distinguées.

•

Paris, le 12 mars 1933.

Cher Monsieur,

J'ai bien suivi le régime de Peyotyl pour la fatigue et la dépression nerveuse.

Je dois dire franchement que je me trouve beaucoup plus actif et à la fin de la journée je ne suis plus du tout fatigué.

Je trouve que les petites doses me font plus d'effet en les prenant régulièrement bien entendu.

Veuillez agréer, Cher Monsieur, mes salutations les plus distinguées.

•

Paris, le 17 mars 1933

Monsieur,

J'ai le plaisir de vous informer que la cure de Peyotyl R. D. que j'avais commencée pour mon état nerveux a complètement réussi.

Je connais à nouveau des nuits calmes, sans cauchemars et je me trouve le matin la tête reposée et claire alors que les somnifères que j'avais employés jusqu'ici me laissaient engourdie et inapte à toute activité.

Toutes mes obsessions ont disparu et je me sens pleine de confiance pour l'avenir.

Recevez, Monsieur, l'assurance de mes meilleurs sentiments.

MODE D'EMPLOI : Prendre régulièrement deux à quatre dragées par jour avant le repas. Contre l'insomnie, une ou deux dragées avant de se coucher, à une heure d'intervalle.

(Facsimile)

It may be of interest to sum up in this paragraph a case which was examined by the League of Nations Advisory Committee on Traffic in Opium and Other Dangerous Drugs in 1936. A Genevese pharmacy embarked on a large-scale advertising campaign for a product named Peyotyl, for which it claimed remarkable properties, as will be seen from figures 7 and 8, facsimiles of the original handbills. The Advisory Committee, having taken cognizance of them, asked Dr. Carrière, the Swiss member, for his opinion, and he drew the attention of the authorities of the Canton of Geneva to the matter. Subsequently, the Swiss Federal Public Health Service stated that "it would be advisable to allow Peyotyl to be supplied only on medical prescription. It has been proposed to the cantonal health authorities that they should take steps to this end. It would be better, however, for pharmacists not to wait until the cantonal ordinances come into force, but to refuse to supply the drug in question without a medical prescription".[35]

So vanished the drug which was to "restore the individual's balance and calm and promote a full expansion of his faculties".

Many articles examining and describing the effects of peyotl and its alkaloids have been published — for instance, Beringer, Clerc, Critchley, Dixon, Grace, Guttmann, Havelock Ellis, Heffter, Janot, Lewin, Marinesco, Mogilewa, Mooney, Paris, Perrot, Raymond-Hamet, Rouhier, Smythes & Wikler, whose works were consulted by the writers of this article.

What, as some of these authors inquire, is the relation between the effect of the alkaloids taken separately and their effect when taken together? And as with other plants with an alkaloid content, are the effects of the plant when fresh the same as when it is dried, and, again, do not those effects differ from those of the aggregate alkaloids? It would be difficult to give an accurate reply to those questions without extensive tests covering a very large number of subjects (the reactions, especially the psychological reactions, differ appreciably from one person to another) together with experiments on the fresh plant, mescal buttons, each alkaloid and the aggregate alkaloids. So far as is known, this work has not yet been undertaken. Some authors, such as Beringer, have carried out tests on a fairly large number of subjects.[36] Most of them used mescal buttons or mescaline. Far fewer authors worked on the fresh plant, and what they usually did was to observe ritual consumption rather than to undertake systematic experiments.

Luckily, it seems possible to draw a general conclusion from the literature as a whole: most authors agree that the effect of peyotl is essentially the same as that of mescaline, and the observations relating to that substance (in almost all cases synthetic mescaline) agree with those concerning fresh peyotl or mescal buttons.

* * *

The purely physiological effects of peyotl will first be examined, then the psychological effects of peyotl and mescaline together, since a separate study of each of them would cover the same ground twice over.

[35] Quoted in *Journal de pharmacie*, Brussels, 14 June 1936.
[36] Op. cit.

Peyotl (mescal buttons). Mescal buttons are usually chewed (see above) or less frequently taken in an infusion — so-called peyotl tea. The taste is bitter. The amount required to obtain an effect seems to be four buttons (about 12 g). Mooney speaks of an Indian who absorbed 90 buttons straight off, or about 225 g, equal to more than 10 g of aggregate alkaloids, which seems an enormous quantity. With most subjects an emetic effect appears after five or six buttons. After some time a certain muscular relaxation is usually noted; the subject finds it hard to co-ordinate his movements. His breathing becomes slower. Other effects noted include cardiac depression, frequent headaches and a dry skin with itching. Despite certain assertions, peyotl seems to be an anaphrodisiac. Peyotl intoxication may last from four to five hours on an average (the length obviously depends on the individual and on the amount taken). The after-effects of peyotl intoxication are slight: a certain indolence, accompanied by headache and, according to some authors (Havelock Ellis, Putt), persistence of the visual hyperaesthesia.

Mescaline. By far the most important of the peyotl alkaloids, inasmuch as it is the main agent of the effects of peyotl itself and also because of its own properties. Main effect: depression of the central nervous system; progressive paralysis, stoppage of respiration and abolition of reflexes (experiments with frogs) — effect on the muscular system: progressive paralysis — effect on the circulation: lowering of blood pressure, weakening of heartbeat. On respiration: slowing of the rhythm, leading to almost complete stoppage. It causes contractions of the intestines and of the uterus *in situ.*

Psychological Effects

A great many authors have described the psychological phenomena due to peyotl and mescaline, usually with a narration of the events as they occurred (by shorthand, dictaphone). There is therefore a fairly large mass of material, a summary of which would exceed the limits of this article. One of the best-known of these interpretations is Aldous Huxley's work, *The Doors of Perception.*[37]

The fact should be clearly borne in mind that, even though the form of the hallucination is fairly constant, its content depends primarily on the individual concerned. A subject without musical experience would very probably fail to hear the symphonies described by certain authors. Similarly, a subject having no skill in painting would not have the same kind of coloured vision as a painter, for whom colour is one of the basic elements of life. Thus, most subjects who have been asked to describe what they have seen were unable to do so, or simply resort to commonplaces (" It's marvellous "; " I see blue lines "). On the other hand, when Marinesco[37] conducted his experiment on a professional painter, the latter depicted his visions, but " the mescaline did not alter his style of painting. It was his own temperament and his own predilections which were expressed in the images depicted, although in an exaggerated form ". In other words, mescaline, contrary to many simple-minded assertions, creates nothing.

[37] Op. cit.

Bearing this in mind, one or more of the following effects are usually observed:

Visual hallucinations. Colours are at first intensified — gradually the subject shuts his eyes and entoptic phenomena appear, followed by true hallucinations with forms, shades and movements. Complete scenes are seen.

Auditory hallucinations. Fairly rare, but frequent correspondences of colour, music and form: " making the sound of a flower opening " — frequent hypersensitivity and pain at the slightest noise.

Abnormal touch, taste and smell. Paresthesias, alteration in perception of heat and cold. The subject often complains of a bad smell in the room or a bad taste in his mouth.

Disturbances in the perception of the subject's own body: feeling that he is changing shape. Inability to locate some part of the body;

Disturbances of the perception of space and time. The subject sees infinitely long corridors or decides that he cannot grasp some object because it is too far away, whereas it is actually within reach (feeling of seeing the world through the wrong end of an opera-glass). Similarly " stretching out " of time, seconds seeming to last hours.

Synesthesia. All the senses seem to follow the same rhythm, and any change in the music changes the colour of what is seen, the taste in the mouth, etc.

With regard to the emotional state, an ecstatic euphoria with laughter is usually observed, especially at the beginning of the intoxication. This state is sometimes followed by anxiety and — less frequently — depression. The subject then becomes suspicious and hostile, especially towards the person conducting the experiment.

Lastly, perhaps the most important effects of mescaline (and peyotl) are the *personality disturbances:* duality of the person — the subject observes himself as if he were two persons; loss of the sense of the ego and of reality.

Disturbances of the will: the subject speaks words and makes gestures which he simultaneously does not wish to speak or make. Lastly, *disturbances in logical thinking:* the subject cannot pursue an idea. Guttmann[38] reports that some subjects were given tests to check concentration, reasoning and judgement, and the failures were conclusive.

* * *

Habituation and Addiction

It now has to be considered whether peyotl and mescaline cause habituation and addiction. Very few of the authors consulted assert that they produce such effects. Critchley[39] is almost the only one who states definitely that they do. Some say that no opinion can be formed, but believe it is possible that habituation to mescaline may occur. Most of the authors consulted, however, including scientists, chemists, doctors and ethnologists long familiar with these substances, state roundly that they do not cause either habituation or addiction.

[38] E. Guttmann: *Artificial Psychoses* ..., op. cit.
[39] Op. cit.

Guttmann [40] states: " Experience has shown that the authors who thought that the pleasant state of intoxication produced by mescaline would speedily lead to addiction were wrong." Rouhier [40] states: " Since the use of peyotl does not produce euphoria in the strict sense of the term and does not lead to habituation, there seems to be no reason for preparations of it to be included in the group of narcotic drugs." Slotkin [40] says: " The habitual use of peyotl does not seem to produce tolerance or accrued dependence." The same opinion was also expressed by the group of scientists who, in a statement made to the journal *Science* (13 November 1951) affirmed that peyotl was not a narcotic drug. They included Dr. Weston, La Barre, Duke University; Dr. D. P. McAllester, Wesleyan University, Dr. O. C. Stewart, Colorado University and Prof. S. Tax, Chicago University. However, Dr. Ellenberger, a psychiatrist who has taught at the University of Topeka (Kansas) and who knew a group of Indian members of the Native American Church very well, has stated in a note to the Division of Narcotic Drugs that he personally knew an Indian who had become a " peyotl addict ". Nevertheless, such habituation seems to be purely psychological.

* * *

Quasi-medical Use

As was pointed out above, there are practically no therapeutic uses of peyotl and its alkaloids in modern medicine.

With regard to the Mexican Indians and, at a later date, the Indians in the United States who believe in the mystical virtue of peyotl, it is hard to decide whether they began by experimenting with its therapeutic uses and then went on to worship it, or whether, conversely, it is because they believe in its mystical virtue that they use it as a remedy, in accordance with a well-known tendency of primitive mentalities: sickness, they believe, has no physical cause, but is a manifestation of the wrath or malignity of the spirits or the divinity. Hence, any distinction between the use of peyotl as a remedy and its part in a cult is artificial.

The best way to draw such a distinction is perhaps first to consider the *use of peyotl by individuals* for their personal ends and then its collective use.

The Indians use peyotl individually for all kinds of purposes: first, as a stimulant to allay the sensation of hunger and fatigue; secondly, as a remedy for the most varied ailments and accidents — to counteract the effects of snake-bite; macerated in alcohol, against rheumatism (massage); directly or in a decoction to cure headache, haemorrhages and fevers; as a cure for tuberculosis. Thirdly, they use it as an amulet for protection against accidents or as a drug to induce prophetic visions; lastly, sometimes simply as an intoxicant, exactly like alcohol elsewhere.

Cult Uses

Collective uses are of two kinds: first, as an accessory in certain tribal rites, when peyotl is a means of attaining a state of trance, for example; and secondly, symbolically in the ornaments used in feasts and ceremonies. It then forms part of the propitiatory rites for rain. These rites, which are very complicated and were formerly widespread among certain Mexican Indian tribes, are gradually dying out. A study of them would exceed the limits of this article. Very accurate and remarkably illustrated descriptions (including the music to accompany the hymns) will be found in Lumholtz [41] (especially for the Huichols) and A. Rouhier.[42]

The last use of peyotl to be considered is that of the Native American Church, not as an accessory, but as an integral part of the cult.

There has often been a tendency to slander this cult by describing it as a succession of orgies, etc., the more so as it is little known and seems strange. Actually, the peyotl cult represents a survival of certain traditions of the Indian tribes. It was established by an Indian *élite*, the leaders of the rest of the flock. The " peyotists " really seem to be seeking in the cult a sort of reaffirmation of their " Indian-ness ". The rites, and even the beliefs, vary from tribe to tribe, but the essential features of this religion may be summed up in a few principles. A very full description of them is given in the monograph by J. S. Slotkin.[43] According to this author, these principles are: (*a*) there is a great spirit who has created the universe and controls the destinies of everything in it, including man; the great spirit has placed part of his supernatural power (*mana*) in peyotl, which he has given to the Indians to help them in their present precarious situation; (*b*) by eating the peyotl under the prescribed ritual conditions the believer absorbs part of the power of the great spirit. The requirements are physical and spiritual purification. The rite is composed of prayers and hymns, the mescal buttons and peyotl tea being distributed to the faithful, who take as much as they wish; (*c*) the power absorbed with the peyotl has spiritual effects. The believers spend a night of watching and prayer and await the divine revelation. The coloured visions are not regarded by the believers as important. The idea is, essentially, to forget the outside world in order to concentrate on the contemplation of the divinity.

Research on the Possible Use of Mescaline in Psychiatry

A final aspect of the matter should be briefly mentioned. This is a use of mescaline which is at present in the experimental stage, but might assume importance in psychiatry and neurology. The bibliography to this article shows the very large number of books dealing with mescaline published in recent years. The aim of most of these is, for the time being, to clear up various obscurities in the action of mescaline. Even a succinct digest of the various directions taken by this research would exceed the scope of this article. Among recent works the following are of special interest: Fischer, Denber, Metlis & Hunter, Hoffe, Osmond & Smythies, Wikler, Hoch, Stockings,[44] etc.

[40] Op. cit.

[41] *Opera citata.*

[42] A. Rouhier : *Le Peyotl*, op. cit.

[43] J. S. Slotkin : *Menomini Peyotism*, op. cit.

[44] *Opera citata.*

Interest in mescaline, as in other similar substances, has been aroused by the effects described above: everything happens as if the substance *created* psychoses and changed the very essence of personality (schizophrenia, paranoiac reactions). By administering a substance of known composition, states met with among mental patients are induced artificially. The first point of interest is to study these states with variations obtained at will by changing the doses, the surrounding conditions and so on, and by auto-observation by the psychiatrist. It is also possible that a similar effect is produced on the patient through some unknown mechanism. Thus, whereas the first research workers to experiment with mescaline were mainly concerned with its effect on the senses, especially the sense of sight, they are now interested in its effect on the personality itself.[45]

[45] See in this connexion the report of the Study Group of the World Health Organization on Ataractic and Hallucinogenic Drugs in Psychiatry. (WHO/AHP/14, 21 April 1958.)

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Any additions or corrections will be welcome; they may be sent to the Division of Narcotic Drugs, Palais des Nations, Geneva, Switzerland.

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The consumption of khat in French Somaliland

by Dr. Kervingant

Khat is not cultivated in French Somaliland, owing to climatic conditions, but it is grown in the neighbouring countries of Yemen and, in particular, Ethiopia, from which it is imported in large quantities. Khat is used only by the men, and as their sole method of consuming it is chewing the fresh leaf, it has to be imported almost entirely by air.

I. *Medical Aspects of the Consumption of Khat*

Although extensive and systematic studies of the pharmacological and physiological, and even of the clinical aspects are lacking, it is doubtful whether the consumption of khat causes addiction in the same way as narcotics.

In the first place, cathine, the alkaloid which gives khat its characteristic properties, has been identified as an alkaloid related to ephedrine-orthedrine. According to the Botanical Laboratory at Bordeaux, the active principle is a tannin-orthedrine complex, similar to the tannin-colative of the cola nut.

Secondly, clinical studies seem to indicate that the physiological effects of khat resemble rather those produced by the cola nut than those produced by the coca leaf. Accordingly, in the case of khat it is probably more correct to speak of habituation than of addiction.

It is estimated that there are about 3,000 khat-chewers in French Somaliland. Actually, the number of patients treated by the medical corps for complaints directly attributable to the use of khat is very small. In three years, only one case has been hospitalized for acute poisoning, and a few cases of intestinal disorders, constipation and frigidity have been treated each year in the dispensaries. All these disorders, even the most serious, are remedied promply by the withdrawal of khat, and there are no after-effects and no internal lesions.

Furthermore, the withdrawal, even if abrupt, does not cause any organic or psychological disturbances; this observation was confirmed at the time when khat was prohibited in the British Somaliland Protectorate, and is corroborated by experience during Ramadan, when the consumption of khat drops sharply. Chronic chewers have said that the withdrawal of khat inconveniences them for a few days, but that they feel no compelling craving for the product.

This seems to prove that the chronic use of khat has no serious direct physiological consequences for the individual, and that it does not result in lesions of the system comparable to those caused by alcoholism, for example.

II. *Social Aspects*

From the social point of view the question is of much greater importance, owing mainly to the cost of the product to the consumer.

It is imported by air; it is subject to export and import duties, and a brisk trade is done in it by middlemen, with the result that a packet of about 250 g of khat, worth about 10 fr CFS at the point of production, is sold to the consumer at between 150 and 250 fr.

Hence, it cannot be said that the cause is escapism due to extreme poverty, for the wage-earner will spend more than half his wage to satisfy his craving.

The money he spends in this way could be much more usefully employed in buying goods which would enable him to live decently.

The social consequences of khat consumption may be summarized as follows.

The use of khat causes loss of appetite, and the weakened system is an easy prey to every acute or chronic disease, of which khat is a predisposing cause. The consequent rise in morbidity is reflected in an increase in social assistance costs.

The worker's mental faculties are numbed; he loses his will to work and suffers from malnutrition, so that his efficiency is low.

The consumer loses interest in his family, which he is, in any case, no longer able to support. The family, too, suffers from malnutrition and also becomes liable to contract various deficiency diseases, or turns for its livelihood to begging, theft or prostitution.

From the genetic point of view, all these deficiencies cause a degeneration of the race; and as khat is said to be an anaphrodisiac, the birthrate may be affected.

Khat does not seem to influence delinquency to any great extent — a consequence of the release of violent instincts which is described by some observers. Most of the cases which come before the courts in connexion with khat arecommercial, cases of debt being the most frequent.

III. *Economic Aspects*

Since khat is not grown in French Somaliland, the prohibition of its cultivation does not raise any economic problems.

The heavy import of the product from neighbouring countries means, however, that a considerable part of the income leaves the country. If this income were used inside the country, economic conditions would undoubtedly benefit, and at the same time the social conditions of the people would improve.

In conclusion, it may be said that the social and economic aspects of khat consumption seem to take precedence over the medical aspects of the plant's use. It is, in any case, desirable that it should be abolished, and for this purpose measures for the gradual prohibition of the use of khat will shortly be adopted in the territory.

The pharmacodynamics of khat

by Dr. Michel Trellu

General

The drug is seen commonly in the form of small bundles of the leafy twigs; these bundles are tied with thin strips of bark, and wrapped up in banana leaves to preserve their initial freshness — the most important quality for the purpose of chewing.

It is a euphoric medicament which, although not containing caffeine, has been compared with caffeic substances — kola, tea, maté, coffee and even coca.

This drug is a native of Arabia Felix; in Yemen three species are cultivated in three different provinces (Saber, Taris and Mogtaria), of which the first two produce a better quality of khat. It has spread enormously in Ethiopia, into which it was first imported in 1429, and where it is now cultivated, and consequently in French Somaliland, where it is merely consumed, and also further south in East Africa.

Historical Background

The khat of the Arabs, which is also called *tschat* or *dimina* by the Gallas of Harar, appears to enjoy divine blessing and the Hararis honour it as a sacred plant. There was even a time when no private or religious ceremony took place without the ritual chewing of the leaf accompanied by much praying and chanting. This (it was reported) induced a state of religious exaltation among the Moslems of Harar, which they regarded as a gift from heaven.

Unlike Moslems, Christian peoples do not use this drug, but merely cultivate it for trade purposes. It is interesting to note, incidentally, that at Harar it is the women who are in charge of the khat fields and that the husbands have nothing to do with this business.

In modern times, it seems that the ritual chewing of khat is no longer important, but it should be noted that the indigenous inhabitants feel an urge to gather in groups of at least five or six persons in order to chew khat while reciting verses from the Koran.

Consumption is none the less considerable; it amounts to 750 kg daily, or 200 tons yearly.

Botanical Characteristics

"*Catha Edulis Forrsk*" belongs to the *celastracae* family, to which the spindle-tree also belongs, and is closely related to the *rhamnaceae* family, the principal member of which is the alder.

It is a shrub of the tea or maté type, thornless, with smooth twigs; its leaves are coriaceous, with short stalks; and it grows mostly on hillsides and mountain slopes in clumps or in beds, and is pruned in order to obtain many young twigs with very tender leaves, which are the best for chewing. The leaves, which are almost tasteless, though slightly bitter and astringent, are 8 to 11 cm long and 2 to 5 cm wide, the median veins and the stalks being slightly reddish in colour.

Khat is propagated by cuttings; its cultivation demands a good deal of care, and — in particular — daily watering and a certain amount of manure. Picking may begin when the shrubs are three years old; only the young twigs are cut off, at the level of the first two small branches. After the picking, the shrubs, which are reduced to a few branches bearing buds, grow for another three years before they are again picked.

These twigs are sold directly to the trade; only the youngest leaves of the central twig, which are greenish-brown in colour, are used for consumption. The leaves of the two lateral twigs are thrown away as being unfit for consumption. (Perhaps they are too tough for chewing, or possibly they do not contain the active stimulating principle.)

Khat is used as a stimulant in two ways: either the *fresh* leaf is chewed or else the leaves are used in preparing local drinks — *talla*, a sort of beer; *tedji*, a sort of wine. A third method is to use the dried leaves for making a refreshing but non-stimulating infusion; the indigenous inhabitants, who want to experience the sensation of euphoria, categorically refuse to take this infusion.

Composition of Khat

This drug consists of resinous and pectic substances, an essential oil, alkaloids, tannin, choline and mannite.

The aromatic essential oil, which has a pleasant odour slightly reminiscent of that of coal tar, is a pale yellow liquid, warm to the taste. It turns brown when exposed to the air and leaves a deposit of pearly crystals of an agreeable odour, resembling that of methyl eugenol.

There are three alkaloids — two amorphous alkaloids (cathinine and cathidine), whose properties are so far unknown; one crystallized alkaloid (cathine $C_{10}H_{18}N_{20}$), to which khat owes its spectacular properties.

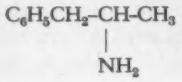
Cathine was identified by Wolfes in 1930 with d-nor-pseudo-iso-ephedrine which is a demethylated ephedrine and an oxidated orthedrine. Cathine is soluble in ether and chloroform, and its salts are soluble in water; accordingly, cathine should be classed as one of the usual alkaloids.

Extraction

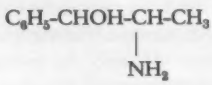
Cathine is extracted by means of chloroform in the presence of diluted ammonia. The solution is then concentrated and shaken with hydrochloric water. It is precipitated again with ammonia, and a white precipitate is obtained which is recrystallized by precipitation in an alcohol and chloroform mixture.

Cathine, which is a very hygroscopic powder, is soluble in ordinary organic solvents, and turns violet upon the addition of sulphuric acid together with potassium bicarbonate (identical reaction to that of strychnine).

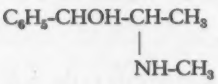
Orthedrine: sulphate of pseudo-1-amino-2-propane



Cathine:



Ephedrine:



Pharmaceutical Properties

Cathine is, as a matter of fact, only slightly toxic, at least for Europeans.

Tests have been carried out on various laboratory animals — in weak doses it induces only a slight excitation of voluntary movements, without increasing reflex excitability up to the stage of mechanism, or producing muscular rigidity, which occurs in tests with caffeine.

If a sub-lethal dose is administered there is at first excitability — the animal jumps about, foams at the mouth and then calms down. Respiratory movements cease, muscles relax, and symptoms of limp paralysis appear; sensitivity is retained, motor action and reflex excitability disappear; the heart slows down and then stops in systole.

In *guinea pigs and rabbits* similar phenomena are more marked, and after an injection of 3-4 cg/kg death occurs in three or four hours, accompanied by convulsions and early muscular rigidity.

If non-lethal doses are administered, signs of excitation with slight motor incöordination and dilation of the pupils are noticed (this may seem paradoxical, since it appears that the pupils of a human being under the influence of khat do not dilate). Respiratory movements are accelerated and the temperature rises by 1 to 3 degrees. Furthermore, a phenomenon pointing to the effect on temperature is observed on the quays of Djibouti: men under the influence of khat sometimes — even in midsummer and in the noon-day sun — feel the need to warm themselves by a wood fire; this is definite evidence of a rise in body temperature.

Cathine therefore particulary affects the nervous system.

To sum up: this drug has, firstly, the primary nervine properties of cocaine, resembling in small doses those of morphine (without, however, possessing the latter's local anaesthetic and analgesic properties) and, secondly, tonicardiac and tonimuscular properties closely related to those of cocaine.

Its psychological effect on man is that of an euphoria-producing stimulant; it facilitates the metabolism without increasing diuresis. Khat acts through the oxidation of fatty substances and tissues, and momentarily accelerates the blood circulation. It thus stimulates man to work, suppresses the desire for sleep and the sensation of fatigue in workers. In the first stage ideas are clear and the brain works fast — the individual finds it easy to carry out his plans, is fresh, willing and hard-working (khat quickens the reactions).

Its abuse causes intoxication, a dazed condition (which is often noticed among Somali " boys ") and cardiac disorders. The intellectual faculties of the indigenous inhabitant are seriously impaired by khat.

The effect of khat from the sexual point of view seems to be to dull desire. Khat acts like coffee, which according to Trousseau is one of the most potent anaphrodisiacs. Its habit-forming properties — as may be observed in the individual — are manifest, and it is for this reason that khat has been called a narcotic drug, but it is not so addictive as morphine. When the British, from one day to the next, strictly prohibited the use of khat in British Somaliland, no organic disorders were observed among the Aberahoual.

The use of khat removes the sensation of hunger, and this explains why most khat consumers are so thin.

Consequently, both from the sexual and intellectual points of view, and also from that of nutrition, khat may be regarded as a sort of social scourge. It causes the degeneration of the race in several respects, and work becomes increasingly distasteful to the khat chewer. Thus, although not poisonous in itself, khat must be regarded as a poison by reason of the consequences of its consumption.

The question now is whether the use of khat should or should not be prohibited. Opinions are divided. From the human and social points of view, as has been said above, it is a sort of scourge which should be eliminated, at least gradually.

From the economic point of view, so far as French Somaliland is concerned, it is obvious that the 10 million fr which the sales tax on khat yields annually are not to be scorned. The consumption of khat accounts for an annual sum of 170 million Djibouti fr; the Ethiopians charge a tax of 160 fr ($2) per k, and the French a special tax of 35 fr plus excise duty of 30 fr payable on the arrival of the daily aircraft from Addis Ababa, or at Ali-Sabieh, where the Franco-Ethiopian railway crosses the frontier.

In addition, there is the illicit traffic, which amounts to approximately 10% of the lawful trade.

On the other hand, as Mr. Roche, the former Procureur de la République at Djibouti, said, since the oriental is very fond of this narcotic, it is not impossible that an even more harmful substance might make its appearance, if khat were prohibited.

World Health Organization

Expert Committee on Addiction-producing Drugs: Ninth Report [1]

The Expert Committee on Addiction-producing Drugs of the World Health Organization held its ninth session in Geneva from 6 to 11 October 1958 and made a report which was noted by the Executive Board of the World Health Organization at its twenty-third session, held in Geneva from 20 January to 3 February 1959 (resolution EB 23. R21, Official Records of the World Health Organization, *1959, 91).*

Extracts from this report are reproduced hereafter with minor modifications. Actions modifying the scope of the international control of narcotic drugs, such as placing a new drug under control or removing it from control, will not be reported here, but in the note *at the end of the present number of the* Bulletin.

Work of International Bodies concerned with Narcotic Drugs

The Secretary summarized the report of the thirteenth session of the Commission on Narcotic Drugs of the Economic and Social Council; [2] the relevant resolutions of the Economic and Social Council; [2] and the reports on sessions of the Permanent Central Opium Board [3] and the Drug Supervisory Body.[3] Among the items of interest, particular note was taken of the publication of the *Multilingual List of Narcotic Drugs under International Control*,[4] which should be invaluable to all concerned in this field. The Committee was pleased to know that it was hoped to keep the list up to date by appropriate supplements, and its members would be prepared to assist in this work.

The value of the United Nations document " Supplementary information on synthetic and other new narcotic drugs "[5] was recognized. The Committee emphasized that expressing consumption of drugs in terms of therapeutic doses instead of in gross amounts enabled a more realistic assessment to be made of their relative uses.

The Committee was pleased to note that there was increasing acceptance of the principle, set out in its sixth report,[6] of making no distinction, for the purposes of control, between the group of natural alkaloids and their derivatives on the one hand and the group of synthetic substances on the other.

Abuse of Non-opiate Analgesic Mixtures

The attention of the Committee was drawn to certain mixtures, containing phenacetin and other agents such as aminophenazone, caffeine and a sedative, which are potentially habit-forming and which under conditions of excessive use have presented characteristics approaching those of addiction. Their prolonged use and potential misuse should be followed closely for an eventual valuation of their effect on public safety.

Non-addicting Antitussives

The Committee discussed the steadily increasing consumption of codeine and dionine as reported by the Permanent Central Opium Board [7] and the Drug Supervisory Body,[7] which it does not seem possible to account for solely by population increases. It may be due largely to the increasing use of codeine in analgesic mixtures, but partly also to the use of codeine and dionine as antitussives. In this connexion, the Committee would draw attention to the development of methods for the evaluation of antitussive action, through which it has been demonstrated that such action can be produced by agents which are neither analgesic not addicting. Outstanding examples are noscapine [8] and dextromethorphan. Other non-analgesic substances (including possible non-analgesic optical isomers of analgesic synthetics) are likely to possess similar action. Investigation and use of non-addicting antitussives should be encouraged, with a view to helping the prevention of drug addiction.

Measurement of Tolerance and Physical Dependence in Clinical Practice

The Committee received a report on the employment of a new technique to determine the development of physical dependence when analgesics are used in the treatment of chronic pain.[9] Periodic administration of nalorphine in fixed relation to an analgesic dose was the tool, and the drugs compared were morphine, oxymorphone, and anileridine. The Committee considered the work of very great importance as a complement to the Lexington addiction liability studies on post-addicts, and was pleased to learn that the new method will also be employed in the study of other analgesic drugs.

Classified Information on Narcotics

Two years ago, the Expert Committee on Addiction-producing Drugs [10] commented upon the desirability of having available a centralized source of information on drug addiction, if possible in the form of abstracts of published

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[1] *WHO Technical Report Series* (1959), No. 160.
[2] See *Bulletin on Narcotics*, Vol. X, No. 4.
[3] See *Bulletin on Narcotics*, Vol. X, No. 1.
[4] *Multilingual List of Narcotic Drugs under International Control* (document E/CN.7/341).
[5] *Supplementary Information on Synthetic and Other New Narcotic Drugs* (document E/CN.7/339).
[6] See *Bulletin on Narcotics*, Vol. VIII, No. 1.
[7] See *Bulletin on Narcotics*, Vol. X, No. 1.
[8] International non-proprietary name proposed for narcotine.
[9] See article by Drs. N. B. Eddy, L.E. Lee & C. A. Harris, *Bulletin on Narcotics*, Vol. XI, No. 1, p. 3.
[10] See *Bulletin on Narcotics*, Vol. IX, No. 1.

papers. A year later,[11] the Committee was informed of the possibility of establishing such a collection of information, because support had been afforded by the National Institute of Mental Health, Bethesda, Maryland, United States of America, the intent being to deal with all aspects of addiction-producing and habit-forming drugs, including relevant experimental, clinical, and statistical data.

It has been found that a complete abstracting service is not possible, at least at the present time. However, work has begun on the collection of all available information (reprints, official documents, manuscripts, abstracts, etc.). This material will be entered bibliographically on a Keysort card. Also, according to an established code, the items of information (drugs described, drug effects, modifying factors, tolerance, habituation and addiction) in each piece of collected material will be indicated on the card together with the relevant code numbers. These code numbers will be punched on the margin of the card to facilitate the finding of data on a particular subject.

The collected documents are being kept at the National Institutes of Health, Bethesda, Maryland. As a contribution to this collection, it is hoped that the members of the Expert Advisory Panel on Addiction-producing Drugs, or any others interested, will make available to the Chief, Section on Analgesics at the National Institutes of Health, either directly or through the Chief, Addiction-producing Drugs Section, World Health Organization, copies of their own papers in the field of narcotics and any other material, duplicate reprints, etc., which they can spare.

The main file of Keysort cards will be prepared and kept at Bethesda. A duplicate set of the index cards will be kept in the Addiction-producing Drugs Section, World Health Organization, Geneva. Photocopies from which Keysort cards may be prepared as well as photocopies of original material will be furnished on request, as far as possible, the purpose being not only to establish the collection, but also to facilitate its availability.

Unification of Chemical Nomenclature for Narcotic Drugs

In view of the procedure now in regular operation for the coining of proposed international non-proprietary names for narcotic drugs, the Committee considered that such names should always be used to designate these drugs. Where it was necessary to use a chemical name, the nomenclature adopted should be identical with that placed opposite the proposed international non-proprietary name in the published lists[12] or consistent with the principles which have been applied to other drugs in these lists if no such name had been published.

In this connexion, the "Multilingual list of narcotic drugs under international control", and any supplements thereto, may be of assistance in finding the appropriate chemical nomenclature of a drug known by another description.

Carriage of Narcotic Drugs in First-aid Kits of Aircraft engaged in International Flight

The Committee's attention was directed to the discussion on the above subject appearing in the report of the thirteenth session of the Commission on Narcotic Drugs and to the relevant resolution of the Economic and Social Council.[13] The Committee considered that such carriage might be permitted provided that (1) there was evidence of the medical need for narcotics in the circumstances of air travel, and (2) an adequate system of control could be ensured.

Proposed Single Convention on Narcotic Drugs

The Committee received the third draft[14] and welcomed the opportunity to make a number of comments which will be considered by the Executive Board.

Treatment of Drug Addicts

The Committee believed that drug addiction, whatever its incidence, is always a serious problem which should be handled medically, as outlined by the report of the Study Group on Treatment and Care of Drug Addicts.[15] It is desirable to make treatment compulsory in the sense that it should always be undertaken, but the Committee believed that the treatment need not necessarily be in a closed institution.

[11] See *Bulletin on Narcotics*, Vol. X, No. 1.

[12] i.e., the *List of Drugs under International Control*, a United Nations document issued yearly as an addendum to the Report of the Division of Narcotic Drugs (the last one is document E/CN.7/356/Add.2, 28 January 1959). Also the lists of international non-proprietary names published from time to time in the *WHO Chronicle*.

[13] See *Bulletin on Narcotics*, Vol. X, No. 4.

[14] The Single Convention on Narcotic Drugs (Third Draft) (document E/CN.7/AC.3/9).

[15] See *Bulletin on Narcotics*, Vol. IX, No. 3.

NOTE

Changes in the Scope of Control

The international treaties on narcotic drugs make provision for changes in the scope of control by means of a procedure which involves governments, the Secretary-General of the United Nations and the World Health Organization, in particular its Expert Committee on Addiction-producing Drugs. The procedure may be applied not only in respect of the extension of control to new drugs, but also in respect of exemption from control of drugs or their preparations.

The international procedure for extending control to new drugs or exempting drugs from control is put into motion upon an application being made by a government to the Secretary-General of the United Nations. Such an application is, however, not necessary in the case of exemption of preparations and of extension of control under articles 8 and 10 of the International Opium Convention, signed in Geneva on 19 February 1925.

During 1958, several requests were received from governments regarding extension of control to new drugs or exemption of certain preparations from control. The following decisions were made by the World Health Organization:

(*a*) The drugs dimenoxadol, normorphine, levomoramide and their respective salts should be placed under the more severe of the two principal regimes of control applying to narcotic drugs — viz., under that which is applicable to morphine or morphine-like drugs, in view of their dangerous addiction-forming properties. It may be noted that the drug levomoramide and its salts had previously been placed provisionally under the same control regime by the Commission on Narcotic Drugs at its thirteenth session, 28 April to 30 May 1958;

(*b*) The drug nicomorphine, being an ester of morphine, was automatically subject to the same regime of control as that applying to morphine or morphine-like drugs;

(*c*) The requests for exemption from control of certain preparations containing the drugs normethadone and dioxaphetyl butyrate, both of which are already under the international control regime applicable to morphine or morphine-like drugs, should not be granted in view of the possible dangers involved;

(*d*) The drug norcodeine, having only slight addiction-producing properties comparable to those of codeine and being not convertible into an addiction-producing drug with morphine-like effects, could not legally be placed under international control; however, it was recommended that this drug be controlled in the same way as codeine, which is subject to the less severe of the two principal control regimes governing narcotic drugs;

(*e*) In reviewing the previous decision taken in 1955 with regard to the drug propoxyphene, it was concluded that for the same reasons as those applying to norcodeine, propoxyphene could not legally be placed under international control. However, it was recommended that this drug be controlled in the same way as codeine;

(*f*) In view of clinical experience having shown that the addiction-producing potentiality of oxymorphone was less than had been anticipated and that it might be considered comparable to morphine, and that in some circumstances oxymorphone had medicinal advantage, the opinion was expressed that restrictions on the manufacture, import and export of oxymorphone needed not be more severe than those applicable to morphine-like drugs. This means that the recommendation made by the World Health Organization in 1954 that it was desirable to avoid the manufacture of and trade in oxymorphone in view of its particularly dangerous addiction-producing properties need not be implemented any more. This recommendation was made by the World Health Organization at the same time at which it decided to place oxymorphone under the regime applicable to morphine;

(*g*) No decision was made in respect of:

(-) 3-Hydroxynormorphinan

2'-Hydroxy-2,5,9-trimethyl-6,7-benzmorphan

3-Allyl-1-methyl-4-phenyl-4-propionoxypiperidine

2-piperidinomethyl-7-benzoylbenzodioxane

2-morpholinomethyl-7-benzoylbenzodioxane

2-piperidinomethyl-7-(p-methoxybenzoyl) benzodioxane

2-morpholinomethyl-7-(p-methoxybenzoyl) benzodioxane.

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